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Antibiotics to prevent complications following tooth extractions (Review)

Lodi G, Azzi L, Varoni EM, Pentenero M, Del Fabbro M, Carrassi A, Sardella A, Manfredi M

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[Intervention Review]

Antibiotics to prevent complications following tooth extractions

Giovanni Lodi[1], Lorenzo Azzi[2], Elena Maria Varoni[3], Monica Pentenero[4], Massimo Del Fabbro[1], Antonio Carrassi[3], Andrea Sardella[3], Maddalena Manfredi[5]

[1]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy. [2]Department of Medicine and Surgery, Unit of Oral Medicine and Pathology, University of Insubria, Varese, Italy. [3]Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche, Università degli Studi di Milano, Milan, Italy. [4]Dept. of Oncology, Oral Medicine and Oral Oncology Unit, University of Turin, Orbassano, Italy. [5]School of Dentistry, University of Parma, Parma, Italy

Contact: Giovanni Lodi, giovanni.lodi@unimi.it.

A B S T R A C T

Background

The most frequent indications for tooth extractions, generally performed by general dental practitioners, are dental caries and periodontal infections. Systemic antibiotics may be prescribed to patients undergoing extractions to prevent complications due to infection. This is an update of a review first published in 2012.

Objectives

To determine the effect of systemic antibiotic prophylaxis on the prevention of infectious complications following tooth extractions.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health Trials Register (to 16 April 2020), the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2020, Issue 3), MEDLINE Ovid (1946 to 16 April 2020), Embase Ovid (1980 to 16 April 2020), and LILACS (1982 to 16 April 2020). The US National Institutes of Health Trials Registry (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials. No restrictions were placed on the language or date of publication when searching the electronic databases.

Selection criteria

We included randomised, double-blind, placebo-controlled trials of systemic antibiotic prophylaxis in patients undergoing tooth extraction(s) for any indication.

Data collection and analysis

At least two review authors independently performed data extraction and 'Risk of bias' assessment for the included studies. We contacted trial authors for further details where these were unclear. For dichotomous outcomes, we calculated risk ratios (RR) and 95% confidence intervals (CI) using random-effects models. For continuous outcomes, we used mean differences (MD) with 95% CI using random-effects models. We examined potential sources of heterogeneity. We assessed the certainty of the body of evidence for key outcomes as high, moderate, low, or very low, using the GRADE approach.

Main results

We included 23 trials that randomised approximately 3206 participants (2583 analysed) to prophylactic antibiotics or placebo. Although general dentists perform dental extractions because of severe dental caries or periodontal infection, only one of the trials evaluated the role of antibiotic prophylaxis in groups of patients affected by those clinical conditions.

We assessed 16 trials as being at high risk of bias, three at low risk, and four as unclear.

Compared to placebo, antibiotics may reduce the risk of postsurgical infectious complications in patients undergoing third molar extractions by approximately 66% (RR 0.34, 95% CI 0.19 to 0.64; 1728 participants; 12 studies; low-certainty evidence), which means that 19 people (95% CI 15 to 34) need to be treated with antibiotics to prevent one infection following extraction of impacted wisdom teeth. Antibiotics may also reduce the risk of dry socket by 34% (RR 0.66, 95% CI 0.45 to 0.97; 1882 participants; 13 studies; low-certainty evidence), which means that 46 people (95% CI 29 to 62) need to take antibiotics to prevent one case of dry socket following extraction of impacted wisdom teeth.

The evidence for our other outcomes is uncertain: pain, whether measured dichotomously as presence or absence (RR 0.59, 95% CI 0.31 to 1.12; 675 participants; 3 studies) or continuously using a visual analogue scale (0-to-10-centimetre scale, where 0 is no pain) (MD −0.26, 95% CI −0.59 to 0.07; 422 participants; 4 studies); fever (RR 0.66, 95% CI 0.24 to 1.79; 475 participants; 4 studies); and adverse effects, which were mild and transient (RR 1.46, 95% CI 0.81 to 2.64; 1277 participants; 8 studies) (very low-certainty evidence).

We found no clear evidence that the timing of antibiotic administration (preoperative, postoperative, or both) was important.

The included studies enrolled a subset of patients undergoing dental extractions, that is healthy people who had surgical extraction of third molars. Consequently, the results of this review may not be generalisable to all people undergoing tooth extractions.

Authors' conclusions

The vast majority (21 out of 23) of the trials included in this review included only healthy patients undergoing extraction of impacted third molars, often performed by oral surgeons. None of the studies evaluated tooth extraction in immunocompromised patients. We found low-certainty evidence that prophylactic antibiotics may reduce the risk of infection and dry socket following third molar extraction when compared to placebo, and very low-certainty evidence of no increase in the risk of adverse effects. On average, treating 19 healthy patients with prophylactic antibiotics may stop one person from getting an infection. It is unclear whether the evidence in this review is generalisable to patients with concomitant illnesses or patients at a higher risk of infection. Due to the increasing prevalence of bacteria that are resistant to antibiotic treatment, clinicians should evaluate if and when to prescribe prophylactic antibiotic therapy before a dental extraction for each patient on the basis of the patient's clinical conditions (healthy or affected by systemic pathology) and level of risk from infective complications. Immunocompromised patients, in particular, need an individualised approach in consultation with their treating medical specialist.

PLAIN LANGUAGE SUMMARY

Are antibiotics an effective way to prevent infection following tooth removal?

What is the problem?

Teeth that are affected by decay or gum disease or painful wisdom teeth are often removed (extracted) by dentists. Tooth extraction is a surgical procedure that leaves a wound in the mouth that can become infected. Infection can lead to swelling, pain, development of pus, fever, as well as 'dry socket' (where the tooth socket is not filled by a blood clot, and there is severe pain and bad odour).

These complications are unpleasant for patients and may cause difficulty with chewing, speaking, and teeth cleaning, and may even result in days off work or study. Treatment of infection is generally simple and involves drainage of the infection from the wound and patients receiving antibiotics.

Why is this question important?

Antibiotics work by killing the bacteria that cause infections, or by slowing their growth. However, some infections clear up by themselves. Taking antibiotics unnecessarily may stop them working effectively in future. This 'antimicrobial resistance' is a growing problem throughout the world.

Antibiotics may also cause unwanted effects such as diarrhoea and nausea. Some patients may be allergic to antibiotics, and antibiotics may not mix well with other medicines.

Dentists frequently give patients antibiotics at the time of the extraction as a precaution in order to prevent infection occurring in the first place. This may be unnecessary and may lead to unwanted effects.

What did we want to find out?

We wanted to know whether giving antibiotics as a preventive measure reduces infection and other complications after tooth extraction. We also wanted to understand whether antibiotics work differently in healthy people compared with people with health conditions such as diabetes or HIV.

What did we do?

We searched for studies that assessed the effectiveness of antibiotics compared to placebo (sham medicine), given when no infection was present in order to prevent infection following tooth extraction. Studies could include people of any age undergoing tooth extraction.

Where possible, we pooled the studies' results and analysed them together. We also assessed the quality of each study to judge the reliability (certainty) of evidence of individual studies and the body of evidence.

What we found

We found 23 included studies with a total of more than 3200 participants, who received either antibiotics (of different kinds and dosages) or placebo immediately before or just after tooth extraction, or both.

Four studies were conducted in Spain, three each in Brazil, Sweden, and the UK, two in India, and one each in Colombia, Denmark, Finland, France, Poland, New Zealand, Nigeria, and the USA. All but one study included healthy patients in their 20s. Twenty-one studies assessed the removal of wisdom teeth in hospital dental departments, one assessed the removal of other teeth and one assessed complex oral surgery. None of the included studies assessed tooth extraction in general dental practice for the removal of decayed teeth.

Main results

Antibiotics given just before or just after surgery (or both) may reduce the risk of infection and dry socket after the removal of wisdom teeth by oral surgeons. However, antibiotics may cause more (generally brief and minor) unwanted effects for these patients. We found no evidence that antibiotics prevent pain, fever, swelling, or problems with restricted mouth opening in patients who have had wisdom teeth removed.

There was no evidence to judge the effects of preventive antibiotics for extractions of severely decayed teeth, teeth in diseased gums, or extractions in patients who are sick or have low immunity to infection.

How reliable are the results?

Our confidence in the results is limited because we had concerns about aspects of the design and reporting of all of the included studies.

What does this mean?

We did not find studies in patients with depressed immune systems, other illnesses, or in young children or older patients, therefore the results of our review probably do not apply to people who may be at high risk of infection. Also, extractions were mainly carried out by oral surgeons, so the review may not apply to dentists working in general practice.

Another concern, which cannot be assessed by clinical studies (i.e. studies testing new medical approaches in people), is that widespread use of antibiotics by people who do not have an infection is likely to contribute to the development of antimicrobial resistance.

We concluded that antibiotics given to healthy people when they are having teeth extracted may help prevent infection, but the decision to use an antibiotic should be judged on an individual patient basis based on their state of health and possible complications of getting an infection.

How up-to-date is this review?

This is an updated review. The evidence is current to April 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Antibiotic compared to placebo for people undergoing tooth extraction

Antibiotic compared to placebo for people undergoing tooth extraction

Population: people undergoing tooth extraction
Setting: any setting
Intervention: antibiotic
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with placebo	**Risk with antibiotic**				
Postsurgical infectious complications (1st to 14th day)	84 per 1000	29 per 1000 (16 to 54)	RR 0.34 (0.19 to 0.64)	1728 (12 RCTs)	⊕⊕⊝⊝ LOW [1]	Antibiotics may substantially reduce the risk of complications.
Presence of pain (yes/no on 6th to 7th day)	126 per 1000	75 per 1000 (39 to 141)	RR 0.59 (0.31 to 1.12)	675 (3 RCTs)	⊕⊝⊝⊝ VERY LOW [2]	The evidence for the effect of antibiotics on pain is very uncertain. Pain measured on a visual analogue scale (where 0 = no pain) was also measured in 4 studies with 422 participants (MD −0.26, 95% CI −0.59 to 0.07).[3]
Fever (6th to 7th day)	41 per 1000	27 per 1000 (10 to 73)	RR 0.66 (0.24 to 1.79)	475 (4 RCTs)	⊕⊝⊝⊝ VERY LOW [4]	The evidence for the effect of antibiotics on fever is very uncertain.
Dry socket (1st to 7th day)	64 per 1000	42 per 1000 (29 to 62)	RR 0.66 (0.45 to 0.97)	1882 (13 RCTs)	⊕⊕⊝⊝ LOW [5]	Antibiotics may reduce the risk of dry socket (slightly to substantially).
Adverse effects (1st to 7th day)	69 per 1000	101 per 1000 (56 to 182)	RR 1.46 (0.81 to 2.64)	1277 (8 RCTs)	⊕⊝⊝⊝ VERY LOW [6]	The evidence for any adverse effects of antibiotics is very uncertain.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

[1]Downgraded one level for risk of bias and one level for indirectness. Only 2 out of 12 studies had a low risk of bias, and the 3 studies with the highest weight were at high risk of bias. All studies included only extractions of the third molar in young and healthy patients, thus they are not representative of the whole population of people undergoing tooth extraction.

[2]Downgraded one level for risk of bias, one level for inconsistency, and one level for indirectness. All studies included only extractions of the third molar in young and healthy patients, thus they are not representative of the whole population of people undergoing tooth extraction. We assessed two out of three studies as at high risk of bias, and the third study as at unclear risk of bias. We detected significant heterogeneity. The CI crossed the no-effect line, and the studies were small.

[3]Downgraded one level for risk of bias, one level for imprecision, and one level for indirectness. All studies included only extractions of the third molar in young and healthy patients, thus they are not representative of the whole population of people undergoing tooth extraction. The CI crossed the no-effect line, and the studies were small. Only one out of five studies was at unclear risk of bias; the others were at high risk of bias.

[4]Downgraded one level for risk of bias, one level for imprecision, and one level for indirectness. All studies included only extractions of the third molar in young and healthy patients, thus they are not representative of the whole population of people undergoing tooth extraction. Three of the four included studies were at high risk of bias. Only one study had few events, whilst the other three studies had no events.

[5]Downgraded one level for risk of bias and one level for indirectness. All studies included only extractions of the third molar in young and healthy patients, thus they are not representative of the whole population of people undergoing tooth extraction. Only 1 out of 13 studies was at low risk of bias, and the 2 studies with the highest weight were at high risk of bias.

[6]Downgraded one level for risk of bias, one level for inconsistency, and one level for indirectness. All studies included only extractions of the third molar in young and healthy patients, thus they are not representative of the whole population of people undergoing tooth extraction. We detected significant heterogeneity. Five out of seven studies were at high risk of bias, and the other two studies were at unclear risk of bias. The CI crossed the no-effect line.

BACKGROUND

Description of the condition

Tooth extraction is a very common surgical procedure, and is most frequently done by general dental practitioners. In spite of the steady decrease in routine extraction of permanent teeth registered in recent decades (McCaul 2001; Sleeman 1995; Thomas 1994), and a significant decline in the prevalence and incidence of severe tooth loss (Kassebaum 2014), general dental practitioners from European countries may extract up to seven teeth per week (McCaul 2001; Worthington 1999). The highest tooth extraction rate per patient is amongst patients in the sixth and seventh decade of life (Chrysanthakopoulos 2011). The main reasons for extraction of permanent teeth are caries and periodontal disease, in variable proportions according to age of patients and country (see Table 1). Wisdom teeth failing to erupt or erupting only partially represent a distinct category of dental elements named impacted (third molar) teeth. Impacted wisdom teeth are extracted either because of local inflammatory problems, or with the aim of avoiding possible future complications (although a recent Cochrane Review did not find sufficient evidence to support or reject routine prophylactic removal of asymptomatic impacted wisdom teeth in adults) (Ghaeminia 2020)).

For surgery to be considered successful, it should minimise patient discomfort in the postoperative period after tooth extraction as much as possible. Complications such as pain, swelling, trismus, fever, and dry socket are unpleasant for patients and may cause difficulty in chewing, speaking, and performing oral hygiene, and alteration of other activities of daily living, resulting in days off from work or study. All of these complications depend on inflammatory response, but they can be due to subsequent infection, for example if surgical trauma is in a contaminated area (where severe caries or periodontitis is present) or where more complex and aggressive procedures are performed (e.g. ostectomy).

Signs of postextraction infectious complications include abscess, pain, fever, swelling, trismus. Another complication of putative bacterial origin is alveolar osteitis (dry socket), a painful condition that follows the dissolution of the blood clot that occurs as a result of bacterial invasion. The overall incidence of postoperative infections is relatively low (Bortoluzzi 2010; Bouloux 2007; Jaafar 2000); however, antibiotics are frequently prescribed prophylactically, particularly in cases of complex surgical extractions and/or surgical extractions and people with systemic conditions potentially causing immunodeficiency, such as HIV infection, diabetes, and cancer (Epstein 2000).

Description of the intervention

A range of antibiotics are effective, in association with clinical treatment (e.g. drainage of abscess), in treating dental infections, which have been used to prevent dental infections as well. These include amoxicillin, erythromycin, clindamycin, doxycycline, and metronidazole, which are usually administered orally, between one and four times daily. Alternatively, antibiotics can also be administered by parenteral or local routes.

How the intervention might work

The oral environment contains a range of bacteria that have the potential to cause painful infections in wounds, even after tooth extractions. Antibiotics are effective in treating such infections and are also likely to prevent the development of painful wound infections.

Before prescribing an antibiotic for prophylaxis purposes, the clinician should:

1. decide if the prophylaxis is appropriate;
2. determine the bacterial flora most likely to cause postoperative infection;
3. choose an antibiotic with the narrowest antibacterial spectrum required;
4. choose the less expensive drug if two drugs are otherwise of equal antibacterial spectrum, efficacy, toxicity, and ease of administration;
5. administer dose at the right time;
6. administer antibiotics for a short period;
7. avoid antibiotics likely to be used in the treatment of serious sepsis;
8. do not use antibiotic prophylaxis to overcome poor surgical technique;
9. review antibiotic prophylaxis protocols regularly, as both cost and hospital antibiotic resistance patterns may change (Dellinger 1994).

However, the optimal timing of the dose or doses of prophylactic antibiotic therapy is unclear. Antibiotics may be administered as a large single dose prior to the extraction, or as a course of antibiotics taken over the postoperative period, or some combination of these. In addition, adverse effects such as diarrhoea or allergy due to antibiotics are also possible.

Why it is important to do this review

In 2010, a systematic review showed that both long duration and multiple courses of antibiotics prescribed in general medical practice were consistently associated with the development of bacterial resistance, in particular individuals who received more antibiotic courses had a higher chance of developing bacterial resistance to the antibiotic (Costelloe 2010). According to the Centers for Disease Control and Prevention (CDC) report on antibiotic resistance threats, more than 2.8 million antibiotic-resistant infections occur in the USA each year, and more than 35,000 people die as a result (Antibiotic Resistance Threats in the United States). Even when addressing severe orofacial infections, increasing antibiotic resistance has been reported to potentially affect patient outcome (Kim 2017).

According to the European Commission (EU), the overuse and misuse of antibiotics are the main causes of microbial resistance to drugs. For this reason, an action plan to tackle microbial resistance to drugs was presented in 2011, the first aim of which was to ensure that antimicrobials are used appropriately both in humans and animals. A particularly high prescribing habit was reported amongst dentists (Ford 2017; Marra 2016), with just a slight reduction in the last decade (Khalil 2015; Preus 2017; Teoh 2018; Thornhill 2019a). Dental prescribing accounts for a significant proportion of total antibacterial prescribing in primary care (7% to 10%) (Dar-Odeh 2010; Khalil 2015; Preus 2017; Suda 2019; Teoh 2018; Thornhill 2019a). In addition, antibiotics used in dental practice can cause potentially serious adverse drug reactions and interactions (Thornhill 2019). Of note, even in settings for which guidelines are available, there is inappropriate

prescribing, with overuse of prophylactic antibiotic therapy as high as 80% observed (Suda 2019), and the use of amoxicillin/clavulanic acid has recently increased in the UK and Australia (Teoh 2018; Thornhill 2019a). Better evidence is needed regarding the use of antibiotic prophylaxis in people undergoing tooth extraction, in order to determine appropriate use (EU Commission 2011; EU Commission 2019).

There is high heterogeneity amongst studies describing possible complications of dental extractions; the terminology used to classify signs of infection as well as timing of patient evaluation after dental extraction can vary widely between trials. In particular, pain, swelling, and trismus may be present two to three days after dental surgery, which do not represent a sign of infection and may be due to surgical trauma. On the contrary, persistence of signs and symptoms from six to seven days after a dental extraction may be related to the presence of bacterial infection.

This systematic review summarises the evidence on the effects of systemic antibiotics prescribed to prevent infectious complications following tooth extraction. It updates a review published in 2012 (Lodi 2012). A separate Cochrane Review that evaluated interventions to manage dry socket following tooth extraction was published in 2012 (Daly 2012).

OBJECTIVES

- To assess the effects of antibiotic prophylaxis on the incidence of infectious complications following tooth extraction.
- To assess the effects of antibiotic prophylaxis following tooth extraction in immunosuppressed patients (e.g. HIV infection, AIDS, diabetes, transplants) or patients with other conditions (e.g. bone diseases).
- To assess the effects of antibiotic prophylaxis in particular procedures, such as extraction of impacted teeth or wisdom teeth.

METHODS

Criteria for considering studies for this review

Types of studies

We assessed randomised controlled trials (RCTs) with a double-blind design (participants and assessors). We included cross-over studies, providing the interval (or washout period) between interventions was at least six weeks.

Types of participants

Anyone undergoing a tooth extraction, including extraction of impacted teeth.

Types of interventions

Active

Any regimen of systemic antibiotic prophylaxis (i.e. prescribed in the absence of infection) administered before or after tooth extraction. Topical antibiotic therapy was not included.

Control

Placebo.

Types of outcome measures

The main outcome measures considered in this review dealt with postsurgical complications of putative infectious nature.

Primary outcomes

- Postsurgical infectious complications, which may occur with one or more of the following: pain, fever, swelling, trismus.

Secondary outcomes

- Pain at sixth to seventh day.
- Fever at sixth to seventh day.
- Swelling at sixth to seventh day.
- Trismus at sixth to seventh day.
- Dry socket (alveolar osteitis).
- Any adverse event.

We did not consider for inclusion trials that reported the outcomes of endocarditis incidence, bacteraemia, or serum markers of infection only.

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for RCTs and controlled clinical trials without language or publication status restrictions:

- Cochrane Oral Health Trials Register (searched 16 April 2020) (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 3) in the Cochrane Library (searched 16 April 2020) (Appendix 2);
- MEDLINE Ovid (1946 to 16 April 2020) (Appendix 3);
- Embase Ovid (1980 to 16 April 2020) (Appendix 4);
- LILACS BIREME Virtual Health Library (Latin American and Caribbean Health Science Information database; from 1982 to 16 April 2020) (Appendix 5).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid; where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategies designed by Cochrane for identifying RCTs and controlled clinical trials as described in the Technical Supplement to Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2019).

Searching other resources

Cochrane Oral Health's information specialist searched the following trial registries for ongoing studies:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 16 April 2020) (Appendix 6);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 16 April 2020) (Appendix 7).

We checked the reference lists of all eligible trials and existing reviews for additional studies.

We checked that none of the studies included in this review were retracted due to error or fraud.

We did not perform a separate search for adverse effects of interventions used; we considered adverse effects described in the included studies only.

Data collection and analysis

Two review authors performed all steps of data collection and analysis independently, with any disagreements resolved by discussion.

Selection of studies

Two review authors independently examined the title and abstract of each article resulting from the different search strategies. The search was designed to be sensitive and to include controlled clinical trials; these were filtered out early in the selection process if they were not randomised. Where studies appeared to meet the inclusion criteria for this review, or where data in the title and abstract were insufficient to permit a clear decision, we obtained the full report of the study. At least two review authors assessed the full reports to determine whether studies met the inclusion criteria, with any disagreements resolved by discussion. We recorded studies excluded at this or subsequent stages as well as the reasons for their exclusion in the Characteristics of excluded studies table. We prepared a flow chart to summarise the results of the search (Figure 1).

Figure 1. Study flow diagram.


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┌──────────────────────────┐     ┌──────────────────────────┐
│ 2 further studies        │     │ 1847 records             │
│ identified from searches │     │ identified from the      │
│ of reference lists of    │     │ electronic searches      │
│ included studies         │     │ after duplicates removed │
└──────────────────────────┘     └──────────────────────────┘
                                              │
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                                 ┌──────────────────────────┐     ┌──────────────────────────┐
                                 │ 1847 records screened    │────▶│ 1783 records discarded   │
                                 │                          │     │ as not relevant based on │
                                 │                          │     │ title and abstract       │
                                 └──────────────────────────┘     └──────────────────────────┘
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                                 ┌──────────────────────────┐     ┌──────────────────────────┐
                                 │ 64 full-text articles    │────▶│ 43 full-text articles    │
                                 │ assessed for eligibility │     │ excluded, with reasons   │
                                 └──────────────────────────┘     └──────────────────────────┘
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                                 ┌──────────────────────────┐
                                 │ 21 studies met the       │
                                 │ inclusion criteria       │
                                 └──────────────────────────┘
                                              │
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                                 ┌──────────────────────────┐
                                 │ 23 studies included in   │
                                 │ review                   │
                                 └──────────────────────────┘
                                              │
                                              ▼
                                 ┌──────────────────────────┐
                                 │ 19 studies included in   │
                                 │ quantitative synthesis,  │
                                 │ and 4 studies included   │
                                 │ in qualitative synthesis │
                                 └──────────────────────────┘
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Data extraction and management

All studies that met the inclusion criteria for this review underwent 'Risk of bias' assessment and data extraction using a specially designed data extraction form. At least two review authors extracted data independently, entering the data into a spreadsheet. Any disagreements were discussed and agreement reached. When necessary we contacted authors for clarification or missing information.

We recorded the following data for each trial.

- Year of publication, country of origin, number of centres, source of study funding, recruitment period.
- Details of the participants including demographic characteristics and criteria for inclusion and exclusion, type of teeth being extracted and reasons, numbers randomised to each treatment group.
- Details of the type of antibiotic, dose, mode of administration, time of administration relative to the extraction procedure and duration of antibiotic treatment.
- Details of other concomitant treatments - type of anaesthetic, mouth rinses, pain management.
- Details of the outcomes reported, including method of assessment, and time(s) assessed.
- Description of operators.
- Sample size calculation.

Assessment of risk of bias in included studies

Review authors GL, LA, EV, MP, and MM independently assessed the risk of bias of the included trials. The same review authors (GL, LA, EV, MP, MM) independently assessed the full-text papers, unblinded, resolving any disagreements through discussion and consensus. We used the Cochrane 'Risk of bias' tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). It is a two-part tool, addressing seven specific domains:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- other bias.

We completed a 'Risk of bias' table for each included study (see Characteristics of included studies), and presented the results graphically by study and by domain across all studies. For each domain, we entered relevant information from the study in the 'Risk of bias' table, and on the basis of this information, or information gained directly from study authors, assigned a judgement of 'low', 'high', or 'unclear' risk of bias.

We categorised the overall risk of bias of each trial as:

- low if we assigned low risk of bias for all key domains;
- unclear if we assigned unclear risk of bias for one or more key domains; or
- high if we assigned high risk of bias for one or more key domains.

Measures of treatment effect

The primary measure of intervention effect was reduction in the incidence of infectious complications, such as alveolar osteitis (dry socket), pain, fever, swelling, or trismus between the control and intervention groups.

For dichotomous outcomes, we expressed the estimates of effects of an intervention as risk ratios (RR) or odds ratios (OR) if paired, together with 95% confidence intervals (CIs). For continuous outcomes, we used mean differences (MD) and standard deviation (SD) for each group in order to express the estimate of effect as MD with 95% CI. We planned that if studies reported continuous outcomes on different scales, we would use standardised mean difference (SMD) to pool these data in meta-analyses. For paired data (split-mouth studies), we used the generic inverse variance method (Higgins 2017).

Unit of analysis issues

The statistical unit of analysis was the participant.

For studies with more than two control arms, we selected the one we considered most appropriate for comparison.

In the case of split-mouth cross-over trials where each participant had two extraction procedures, these had to be separated by a period of at least six weeks.

Dealing with missing data

Whenever possible, we obtained missing data from tables and graphs. Where data were missing or unclear, we attempted to contact the study authors to request clarification or additional data.

Assessment of heterogeneity

We assessed heterogeneity by inspection of the point estimates and confidence intervals on the forest plots. We assessed the variation in treatment effects by means of Cochran's test for heterogeneity and quantified by the I^2 statistic. We considered heterogeneity statistically significant if the P value was < 0.1. A rough guide to the interpretation of the I^2 statistic is given in the *Cochrane Handbook for Systematic Reviews of Interventions*: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100%, considerable heterogeneity (Higgins 2017).

Assessment of reporting biases

Only a proportion of research projects conducted are ultimately published in an indexed journal and become easily identifiable for inclusion in systematic reviews. Reporting biases arise when the reporting of research findings is influenced by the nature and direction of the findings of the research. We attempted to minimise potential reporting biases, including publication bias, time lag bias, multiple (duplicate) publication bias, and language bias in this review.

Where there were more than 10 studies reporting on a given outcome, we prepared a funnel plot. If there was asymmetry in the funnel plot indicating possible publication bias, we undertook statistical analysis using the methods introduced by Egger 1997 (continuous outcome) and Rücker 2008 (dichotomous outcome).

We attempted to avoid time lag bias, multiple (duplicate) publication bias, and language bias by conducting a detailed, sensitive search, including searching for ongoing studies. There were no language restrictions, and we found translators for potentially relevant trials published in languages other than English.

Data synthesis

We only conducted meta-analysis if there were studies of similar comparisons reporting the same outcome measures. We combined RRs for dichotomous data, and MDs for continuous data, using random-effects models provided there were more than three studies in the meta-analysis. For two or three studies in a meta-analysis, we used the fixed-effect model.

When trials employed more than one experimental group (multi-arm parallel trials), the number of participants in the placebo group was subdivided for each experimental group in the meta-analysis to avoid overcounting.

Subgroup analysis and investigation of heterogeneity

Whenever possible, we undertook subgroup analyses based on time of administration (pre, post, or pre-post procedure) and the presence or absence of people with systemic conditions (HIV, diabetes, cancer, etc.).

Sensitivity analysis

We planned to undertake a sensitivity analysis including only studies at low overall risk of bias, but due to the small number of such studies we did not do so (Gbotolorun 2016; Leon Arcila 2001; Milani 2015).

Summary of findings and assessment of the certainty of the evidence

We developed a 'Summary of findings' table for the main outcomes of this review using GRADEpro GDT software (GRADEpro GDT). We used the mean risk in the placebo groups of the included studies as the assumed risk for each outcome, and calculated the corresponding risk using the RR (or MD) estimate obtained from the meta-analysis. We assessed the certainty of the body of evidence with reference to the overall risk of bias of the included studies, the directness of the evidence, the consistency of the results, the precision of the estimates, the risk of publication bias, and the magnitude of the effect. We categorised the certainty of the body of evidence for each of the main outcomes as high, moderate, low, or very low.

R E S U L T S

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

Our electronic searches identified a total of 1847 references. Two review authors scanned the titles and abstracts of these references and excluded 1783 as not relevant to this review. We retrieved full-text versions of 64 potentially eligible papers and excluded 43 studies after close reading (see Characteristics of excluded studies table). We identified two further studies from searches of reference lists of the included studies. A total of 23 studies met the inclusion criteria for this review (Figure 1).

Included studies

Characteristics of trial design and setting

For a summary of the characteristics of each included study, see Characteristics of included studies.

Of the 23 included studies, four were conducted in Spain (Arteagoitia 2005; Arteagoitia 2015; Lacasa 2007; López-Cedrún 2011), three in Sweden (Bergdahl 2004; Bystedt 1980; Bystedt 1981), three in the UK (Kaziro 1984; MacGregor 1980; Mitchell 1986), three in Brazil (Bezerra 2011; Bortoluzzi 2013; Milani 2015), two in India (Pasupathy 2011; Sekhar 2001), and one each in Colombia (Leon Arcila 2001), Denmark (Ritzau 1992), Finland (Happonen 1990), France (Sixou 2012), Poland (Kaczmarzyk 2007), New Zealand (Barclay 1987), Nigeria (Gbotolorun 2016), and the USA (Halpern 2007).

Twenty-two studies used a parallel-group design, and one was a split-mouth cross-over trial, Bezerra 2011, where each participant had two extraction procedures, which were separated by a period of at least 45 days. Twelve studies had two treatment arms (Arteagoitia 2005; Arteagoitia 2015; Barclay 1987; Bergdahl 2004; Gbotolorun 2016; Halpern 2007; Leon Arcila 2001; López-Cedrún 2011; MacGregor 1980; Mitchell 1986; Ritzau 1992; Sixou 2012); 10 studies had three treatment arms (Bortoluzzi 2013; Bystedt 1981; Happonen 1990; Kaczmarzyk 2007; Kaziro 1984; Lacasa 2007; López-Cedrún 2011; Milani 2015; Pasupathy 2011; Sekhar 2001); and one study had three subtrials, each with two or three arms (Bystedt 1980). The data from these separately randomised subtrials were then combined and were unsuitable for inclusion in meta-analysis.

Characteristics of participants

Twenty-two of the 23 included studies randomised a total of 3206 participants to either an antibiotic or placebo. The remaining study used an unusual design and did not state exactly how many participants were randomised and analysed (MacGregor 1980). Overall, 2583 participants were analysed in this review.

All of the included studies compared at least one antibiotic regimen with placebo in people undergoing dental extraction. Three trials described extraction procedures using general anaesthesia (Halpern 2007; Kaziro 1984; MacGregor 1980).

In 21 of the 23 included studies participants underwent extraction of third molars only. Two studies only included participants who underwent intra-alveolar extractions or complex oral surgery, respectively (Gbotolorun 2016; Sixou 2012). Of the 21 studies that included participants who underwent third molar extraction, 14 included only mandibular third molars (Arteagoitia 2005; Barclay 1987; Bergdahl 2004; Bystedt 1980; Bystedt 1981; Happonen 1990; Kaczmarzyk 2007; Lacasa 2007; López-Cedrún 2011; MacGregor 1980; Mitchell 1986; Pasupathy 2011; Ritzau 1992; Sekhar 2001).

Sixteen studies included participants with impacted teeth only (Arteagoitia 2005; Arteagoitia 2015; Barclay 1987; Bezerra 2011; Bystedt 1980; Bystedt 1981; Halpern 2007; Happonen 1990; Kaczmarzyk 2007; Kaziro 1984; Leon Arcila 2001; MacGregor 1980; Milani 2015; Mitchell 1986; Pasupathy 2011; Sekhar 2001); two studies participants with either impacted or partially impacted

teeth (López-Cedrún 2011; Ritzau 1992); one study participants with only partially impacted teeth (Bergdahl 2004); one study participants with single inferior third molar only (Bortoluzzi 2013); one study participants with "teeth needing surgical extraction" (Lacasa 2007); and one study different surgical interventions (only data from tooth extractions were considered for this review) (Sixou 2012). Finally, only one study assessed the effect of antibiotic prophylaxis in participants who required extraction of any tooth due to caries or periodontal disease (Gbotolorun 2016).

In one trial (Barclay 1987), participants had a history of non-acute pericoronitis, and in another trial (Bergdahl 2004), 41% of participants had pericoronitis at some stage and were entered into the trial "after objective and subjective symptoms of pericoronitis had ceased"; participants in both of these studies were thus likely to be at higher risk of infectious complications. Recent episodes of local infection was a reason for exclusion in two other studies (Lacasa 2007; Sekhar 2001). In the remaining trials, participants were considered healthy at baseline, and systemic conditions, including those causing immunosuppression, were often a reason for exclusion from the trial (see Characteristics of included studies).

Characteristics of interventions

In 21 out of the 23 included trials, the antibiotics were administered orally; one study used intravenous penicillin or clindamycin (Halpern 2007), and one study administered penicillin intramuscularly (MacGregor 1980).

We classified the antibiotic interventions into three groups based on the time of administration relative to the extraction (studies with three or more arms may be included in more than one group).

- Antibiotics given preoperatively only (30 minutes to 2 hours prior to procedure): Bergdahl 2004; Bezerra 2011; Bortoluzzi 2013; Halpern 2007; Kaczmarzyk 2007; López-Cedrún 2011; MacGregor 1980; Mitchell 1986; Pasupathy 2011; Ritzau 1992; Sekhar 2001; Sixou 2012.
- Antibiotics given postoperatively only: Arteagoitia 2005; Gbotolorun 2016; Kaziro 1984; López-Cedrún 2011; Sekhar 2001.
- Antibiotics given both pre- and postoperatively: Arteagoitia 2015; Barclay 1987; Bystedt 1980; Bystedt 1981; Happonen 1990; Kaczmarzyk 2007; Lacasa 2007; Leon Arcila 2001; López-Cedrún 2011; Milani 2015.

The antibiotics selected for use in the studies were amoxicillin (Bezerra 2011; Bortoluzzi 2013; Leon Arcila 2001; López-Cedrún 2011; Milani 2015; Pasupathy 2011; Sixou 2012), a combination of amoxicillin/clavulanate (Arteagoitia 2005; Arteagoitia 2015; Lacasa 2007), or a combination of amoxicillin and metronidazole (Gbotolorun 2016), azidocillin (Bystedt 1980; Bystedt 1981), clindamycin (Bystedt 1980; Halpern 2007; Kaczmarzyk 2007), doxycycline (Bystedt 1980), erythromycin (Bystedt 1980), metronidazole (Barclay 1987; Bergdahl 2004; Kaziro 1984; Pasupathy 2011; Ritzau 1992; Sekhar 2001), penicillin (Halpern 2007; MacGregor 1980), phenoxymethylpenicillin (Happonen 1990), and tinidazole (Happonen 1990; Mitchell 1986).

Details of specific dosage regimens are recorded in the Characteristics of included studies for each study.

Characteristics of outcomes

Seventeen studies investigated pain (Arteagoitia 2005; Arteagoitia 2015; Barclay 1987; Bezerra 2011; Bortoluzzi 2013; Bystedt 1980; Bystedt 1981; Gbotolorun 2016; Happonen 1990; Kaczmarzyk 2007; Kaziro 1984; Lacasa 2007; López-Cedrún 2011; MacGregor 1980; Milani 2015; Sekhar 2001; Sixou 2012). Arteagoitia 2005 and Sekhar 2001 evaluated pain at 2 and 6 days; Arteagoitia 2015, Barclay 1987, Bezerra 2011, and López-Cedrún 2011 at 7 days; Bystedt 1980 and Bystedt 1981 at 2, 5, and 7 days; Happonen 1990 at 6 days; Kaczmarzyk 2007 at 1, 2, and 7 days; Kaziro 1984 at day 4 and 8; Gbotolorun 2016 and Lacasa 2007 at 1, 3, and 7 days; Bortoluzzi 2013 at day 1, 3, 4, and 5; MacGregor 1980 at 4 days; Milani 2015 at 4 and 7 days; and Sixou 2012 at 7 and 21 days.

Eight studies recorded fever (Arteagoitia 2005; Bystedt 1981; Happonen 1990; Kaczmarzyk 2007; Lacasa 2007; López-Cedrún 2011; Milani 2015; Pasupathy 2011): one study reported fever at 24 hours only (Arteagoitia 2005); two studies recorded the presence of fever at 6 to 7 days after surgery (López-Cedrún 2011; Pasupathy 2011); and five studies recorded fever at different time points (Bystedt 1981; Happonen 1990; Kaczmarzyk 2007; Lacasa 2007; Milani 2015).

Six studies included swelling at day 6 to 7 amongst outcomes (Arteagoitia 2015; Bystedt 1981; Kaczmarzyk 2007; Lacasa 2007; López-Cedrún 2011; Sekhar 2001).

Seven studies investigated trismus amongst outcomes (Bortoluzzi 2013; Bystedt 1981; Happonen 1990; Kaczmarzyk 2007; Lacasa 2007; Milani 2015; Pasupathy 2011): 3 studies registered trismus at different days of follow-up (Bystedt 1981 at 2, 5, and 7 days; Kaczmarzyk 2007 at 1, 2, and 7 days; Lacasa 2007 at 1, 3, and 7 days); 3 studies evaluated trismus at 6 or 7 days after surgery (Happonen 1990; Milani 2015; Pasupathy 2011); and 1 study did not report the timing of trismus evaluation (Bortoluzzi 2013).

Six studies reported the development of dry socket with different timings of evaluation (Arteagoitia 2005; Bergdahl 2004; Bortoluzzi 2013; Bystedt 1981; Gbotolorun 2016; Ritzau 1992). In particular, Ritzau 1992 evaluated this complication with a follow-up at 7 days; Arteagoitia 2005 with a follow-up at 7 days and 8 weeks; Bergdahl 2004 with a follow-up between 2 and 4 days after surgery; Bystedt 1981 with a follow-up at 2, 5, and 7 days; and Gbotolorun 2016 with a follow-up at day 3 and 7. One study did not report the exact timing of dry socket evaluation (Bortoluzzi 2013) .

Seven of the 23 included trials reported the presence or absence of adverse effects per participant (Arteagoitia 2005; Arteagoitia 2015; Barclay 1987; Bystedt 1981; Kaczmarzyk 2007; Lacasa 2007; Milani 2015).

Studies without useable data

Four of the included trials did not report data in a form that was suitable for inclusion in meta-analysis (Bystedt 1980; Kaziro 1984; MacGregor 1980; Sixou 2012).

The authors of Bystedt 1980 conducted three independent subtrials, but reported data combining all of these subtrials. We were therefore unable to draw any conclusions because data about experimental and control groups for each subtrial were missing. The authors of Kaziro 1984 did not report the number of participants included in the outcome assessments, but used graphs

to show the percentage of participants with infection, pain, and swelling. Fewer participants in the antibiotic group complained of infection or pain, but there were not estimates of variance, thus the statistical significance (if any) cannot be determined from this report. The trial by MacGregor 1980 compared a single dose of intramuscular penicillin with placebo, followed up the enrolled participants for four days, and only stated that there were not significant differences with regard to pain, swelling, and trismus between antibiotic and placebo groups. Unfortunately, no data were provided to substantiate this claim. The authors of Sixou 2012 did not report the results as they were stated in the "Materials and Methods" section. This paper was interesting because it dealt with the extraction of teeth other than third molars, but it was not possible to analyse the data as reported.

Excluded studies

We excluded 43 studies after the full text of the paper was read by two or more review authors. We excluded 27 studies that were not double-blind (Abu-Mowais 1990; Adde 2012; Arora 2014; Ataoglu 2008; Barone 2017; Busa 2014; Curran 1974; Delilbasi 2004; Foy 2004; Graziani 2005; Grossi 2007; Krekmanov 1980; Krekmanov 1981; Krekmanov 1986; Lombardia Garcia 1987; Lopes 2011; Lyall 1991; Milani 2012; Mitchell 1987; Monaco 1999; Monaco 2009; Poeschl 2004; Samsudin 1994; Sulejmanagić 2005; Uluibau 2005; Walkow 1995; Yoshii 2002); four studies because two antibiotic regimens were compared directly with no placebo-controlled group (Laird 1972; Limeres 2009; Luaces-Rey 2010; Olusanya 2011); three trials because the interventions were not randomly allocated (Fridrich 1990; Osborn 1979; Rood 1979); three cross-over trials because the washout period between interventions was less than six weeks (de Moura 2011; Siddiqi 2010; Xue 2015); and four trials that evaluated topical antibiotics only (MacGregor 1973; Reekie 2006; Stavropoulos 2006; Swanson 1989). We excluded one trial because it evaluated antibiotics in conjunction with a range of dental surgical procedures (not just extractions) (Bargnesi 1985), and one that presented data on bacteraemia outcomes only (Head 1984). For the main reasons for exclusion of each study, see Characteristics of excluded studies.

Risk of bias in included studies

Overall risk of bias

We assessed three included trials as at low risk of bias for all domains (Gbotolorun 2016; Leon Arcila 2001; Milani 2015). We assessed four trials as at unclear risk of bias because information in the trial report or available from the authors was insufficient to determine risk of bias in at least one domain (Arteagoitia 2015; Bortoluzzi 2013; Halpern 2007; MacGregor 1980). We assessed the remaining 16 trials as at high overall risk of bias because each trial was at high risk of bias in one or more domains (Figure 2; Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 2. (Continued)

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
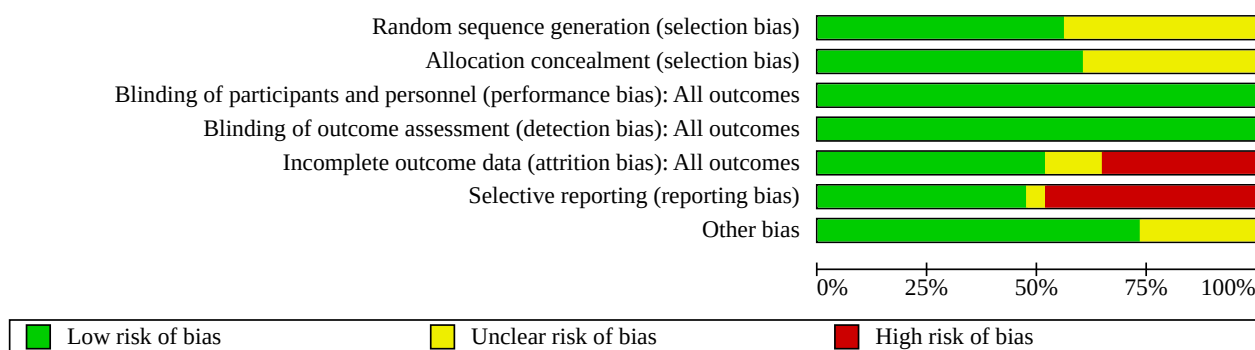
Allocation

Random sequence generation

We assessed 13 studies as at low risk of bias for random sequence generation. Seven studies reported using computer-generated randomisation (Arteagoitia 2005; Arteagoitia 2015; Leon Arcila 2001; Milani 2015; Pasupathy 2011; Ritzau 1992; Sixou 2012); two studies used random number tables (Barclay 1987; Kaczmarzyk 2007); two used predetermined random codes (López-Cedrún 2011; Mitchell 1986); and two studies used a coin toss or picking cards from a box (Bezerra 2011; Gbotolorun 2016). The remaining 10 studies gave no details about the method of sequence generation and were assessed as at unclear risk of bias for this domain (Bergdahl 2004; Bortoluzzi 2013; Bystedt 1980; Bystedt 1981; Halpern 2007; Happonen 1990; Kaziro 1984; Lacasa 2007; MacGregor 1980; Sekhar 2001).

Allocation concealment

Fourteen studies described adequate allocation concealment and were assessed as at low risk of bias for this domain (Arteagoitia 2005; Bezerra 2011; Gbotolorun 2016; Halpern 2007; Kaczmarzyk 2007; Kaziro 1984; Leon Arcila 2001; López-Cedrún 2011; Milani 2015; Mitchell 1986; Pasupathy 2011; Ritzau 1992; Sekhar 2001; Sixou 2012). Allocation concealment was not reported in the remaining nine studies, which we assessed as at unclear risk of bias.

Overall, we considered 11 trials to be at low risk of selection bias (Arteagoitia 2005; Bezerra 2011; Gbotolorun 2016; Kaczmarzyk 2007; Leon Arcila 2001; López-Cedrún 2011; Milani 2015; Mitchell 1986; Pasupathy 2011; Ritzau 1992; Sixou 2012); the risk of selection bias was unclear for the remaining 12 studies.

Blinding

Double-blinding was one of our inclusion criteria, thus all included studies were at low risk of both performance and detection bias.

Incomplete outcome data

Most of the included trials had relatively low rates of participants excluded from the analysis due to loss to follow-up or withdrawal from the trial. However, these trials also reported low event rates for the outcomes of interest, which meant that even small numbers of excluded participants could have introduced bias.

Four trials reported that all the randomised participants were included in the analysis (Bortoluzzi 2013; Bystedt 1981; Leon Arcila 2001; Mitchell 1986). In five trials, attrition was between < 1% and 4%, and losses were equally distributed between study arms (Arteagoitia 2005; Arteagoitia 2015; Bergdahl 2004; Halpern 2007; Milani 2015). Two studies, Gbotolorun 2016 and Sixou 2012, had higher attrition, 12%, and 13% respectively, but they were relatively large in terms of numbers of participants (171 and 250), and the losses were equally distributed between study arms. In the split-mouth cross-over study by Bezerra 2011, two participants were lost to follow-up, but due to the study design, this was not considered to have introduced a risk of attrition bias. We assessed these 12 trials as at low risk of attrition bias.

Three trials did not report the number of randomised participants included in the analysis, and as these trials were published more than 25 years ago, we were unable to obtain this information (Bystedt 1980; Kaziro 1984; MacGregor 1980). We assessed these three trials as at unclear risk of attrition bias.

Four trials reported an overall exclusion of participants from outcome evaluation of between 8% and 17%, and noted that losses were unequally distributed between antibiotic and placebo groups (Barclay 1987; Lacasa 2007; López-Cedrún 2011; Sekhar 2001). A further four trials reported that between 5% and 14% of participants were excluded from the outcome evaluation, and did not describe the reasons for exclusion or the treatment groups from which participants were excluded (Happonen 1990; Kaczmarzyk 2007; Pasupathy 2011; Ritzau 1992) We assessed these eight trials as at high risk of attrition bias.

Selective reporting

Selective reporting is difficult to assess in the absence of a trial protocol. We based our assessment of reporting bias on three factors: whether the trial report contained in the results section, data on all the outcome measures described in the methods section of the report; whether planned outcome measures included those that would reasonably be expected to have been included in such a trial; and whether both point estimates and variances were reported.

Eleven trials reported complete data on all the outcomes that were listed in their methods sections and were thus assessed as at low risk of reporting bias (Arteagoitia 2015; Barclay 1987; Bortoluzzi 2013; Gbotolorun 2016; Halpern 2007; Kaczmarzyk 2007; Leon Arcila 2001; López-Cedrún 2011; MacGregor 1980; Milani 2015; Ritzau 1992).

The authors of Pasupathy 2011 did not mention the outcomes to be evaluated in the patients and methods section, thus we assessed this study as at unclear risk of reporting bias.

We assessed the remaining 11 trials as at high risk of reporting bias because they did not report prespecified outcomes or reported them incompletely so that they could not be entered in a meta-analysis.

Other potential sources of bias

We assessed six trials as at unclear risk of other bias (Bergdahl 2004; Bystedt 1980; Kaziro 1984; Lacasa 2007; López-Cedrún 2011; Sekhar 2001). In one study, the follow-up duration was too short (four days), and it was unclear whether participants who experienced acute pericoronitis before the trial, were treated with antibiotics (Bergdahl 2004). No description of characteristics of participants by randomised group at baseline was available in Bystedt 1980 and Kaziro 1984. In Lacasa 2007 and López-Cedrún 2011, a statistically significant difference in duration of operations between two study arms was recorded. The need for osteotomy was significantly lower in one of the groups in Sekhar 2001.

No other sources of bias were identified in the remaining 17 trials.

Effects of interventions

See: **Summary of findings 1** Antibiotic compared to placebo for people undergoing tooth extraction

The results from the 19 trials providing useable data are described below in subgroups according to the timing of antibiotic administration (preoperatively, postoperatively, or both pre- and postoperatively). For most outcomes, there was either no difference between subgroups or too few studies to evaluate subgroup differences, with the exception of pain measured as a continuous variable. Subgroup analysis based on the immune status of participants was not possible, as studies on immunosuppressed people, or those with underlying health conditions that may have influenced their immune system, were not identified by our searches.

Postsurgical infectious complications

The overall pooled estimate from all 12 parallel-arm RCTs that reported the outcome of postsurgical infectious complications showed that the use of antibiotics reduced the risk of infection (risk ratio (RR) 0.34, 95% confidence interval (CI) 0.19 to 0.64; 1728 participants; 12 studies; I^2 = 28%) (Analysis 1.1). There was no difference between the subgroups (P = 0.10), and the overall meta-analysis heterogeneity was not considered to be important (P = 0.17, I^2 = 28%). The rate of infections ranged from 0 to 56% in the placebo group and 0 to 16% in the antibiotic group. There is a reduction in the risk of infection from a mean of 8.5% (64/757) in the placebo group to 2.6% (27/1035) in the antibiotic group (Table 2).

Preoperative prophylaxis

Eight trials reported the outcome of surgical site infection diagnosed clinically (Bezerra 2011; Bortoluzzi 2013; Halpern 2007; Lacasa 2007; López-Cedrún 2011; Mitchell 1986; Pasupathy 2011; Sekhar 2001). Antibiotics were administered intravenously in one study immediately prior to the procedure (Halpern 2007), whilst in the other seven trials they were administered one to two hours prior to surgery. Seven trials were parallel-arm RCTs (Bortoluzzi 2013; Halpern 2007; Lacasa 2007; López-Cedrún 2011; Mitchell 1986; Pasupathy 2011; Sekhar 2001). In Bortoluzzi 2013, infectious complications were not detected in the antibiotic or the placebo group. The pooled estimate for the other six trials showed a significant reduction in infection in the antibiotic group with an RR of 0.32 without significant heterogeneity (95% CI 0.16 to 0.62; 500 participants; 7 studies; I^2 = 0%) (Analysis 1.1). One study was a split-mouth cross-over study (Bezerra 2011), and was thus not included in the meta-analysis. Bezerra 2011 reported a higher incidence of postsurgical infectious complications in the placebo group (0/34 antibiotic versus 3/34 placebo), but without statistical significance.

Postoperative prophylaxis

Five trials were included in this group (Arteagoitia 2005; Gbotolorun 2016; Lacasa 2007; López-Cedrún 2011; Sekhar 2001). Sekhar 2001 did not record infectious complications in either study group. The pooled estimate for the other four trials showed fewer infections in the antibiotic group (RR 0.21, 95% CI 0.05 to 0.80; 872 participants; 5 studies; I^2 = 37%) (Analysis 1.1).

Pre- and postoperative prophylaxis

In three trials (Arteagoitia 2015; Happonen 1990; Leon Arcila 2001), antibiotics or placebo was administered before and after the tooth extraction procedure. Leon Arcila 2001 recorded no infectious complications in either group. The overall estimate in the subgroup showed no difference between groups in reported infections (RR 0.98, 95% CI 0.38 to 2.52; 356 participants; 3 studies; I^2 = 0%) (Analysis 1.1).

Pain (dichotomous (yes/no) on sixth to seventh day)

The overall pooled estimate from the three parallel arm-RCTs that reported pain as a dichotomous outcome was RR 0.59 (95% CI 0.31 to 1.12; 675 participants; 3 studies; I^2 = 59%) (Analysis 1.2) (Arteagoitia 2005; Bystedt 1981; Sekhar 2001). We detected substantial heterogeneity in the overall meta-analysis and in the postoperative prophylaxis subgroup. The mean rate of the presence of pain at day 6 to 7 was 11.8% (46/390) in the antibiotic group and 12.6% (36/285) in the placebo group (Table 3).

Preoperative prophylaxis

Only one trial employing preoperative prophylaxis reported pain as a dichotomous outcome at day 6 (Sekhar 2001), and found no difference between the antibiotic and placebo groups (RR 1.10, 95%

CI 0.57 to 2.12; 61 participants; 1 study; I^2 not applicable) (Analysis 1.2).

Postoperative prophylaxis

Two trials reported pain as a dichotomous outcome in this subgroup (Arteagoitia 2005; Sekhar 2001). There was no difference in this outcome between antibiotic and placebo groups (RR 0.48, 95% CI 0.15 to 1.52; 554 participants; 2 studies; I^2 = 71%). There was moderate heterogeneity (Analysis 1.2).

Pre- and postoperative prophylaxis

Only one trial reported pain as a dichotomous outcome in this subgroup (Bystedt 1981). Antibiotic prophylaxis was associated with less pain than placebo (RR 0.36, 95% CI 0.13 to 0.98; 60 participants; 1 study; I^2 not applicable) (Analysis 1.2).

Pain (continuous, VAS on seventh day)

Six trials reported pain as a continuous outcome by visual analogue scale (VAS) 0 to 10 cm, where 10 is the most pain (Arteagoitia 2015; Barclay 1987; Bezerra 2011; Kaczmarzyk 2007; López-Cedrún 2011; Sekhar 2001). The trial by López-Cedrún 2011 did not report SD, thus it could not be included in meta-analysis (both preoperative prophylaxis and postoperative prophylaxis), nor could the trial with a split-mouth cross-over design be included (preoperative prophylaxis) (Bezerra 2011).

The mean difference for the four parallel-arm RCTs that reported pain with VAS score showed no statistically significant difference between the antibiotic and placebo groups (MD −0.26, 95% CI −0.59 to 0.07; 422 participants; 4 studies; I^2 = 44%; Table 4) (Arteagoitia 2015; Barclay 1987; Kaczmarzyk 2007; Sekhar 2001). Heterogeneity for subgroup differences was substantial (I^2 = 77.2%; P = 0.01), which could be explained by the fact that trials in the pre- and postoperative prophylaxis subgroup highlighted a protective tendency of antibiotics against pain (Analysis 1.3).

Preoperative prophylaxis

The two trials that reported the VAS score in each group at day 6 to 7 showed no difference between antibiotic and placebo groups (MD −0.10, 95% CI −0.44 to 0.24; 106 participants; 2 studies; I^2 = 0%) (Analysis 1.3) (Kaczmarzyk 2007; Sekhar 2001). The trial by López-Cedrún 2011 did not report SD, thus it could not be included in the meta-analysis; however, the authors reported that VAS pain in the antibiotic group was significantly lower than in the placebo group. Similarly, the trial with a split-mouth cross-over design showed a significantly lower pain level in the antibiotic group compared with the placebo group (Bezerra 2011).

Postoperative prophylaxis

Only one trial reported pain VAS score at day 6 in this subgroup (Sekhar 2001). No differences were recorded between antibiotic and placebo groups (MD 0.10, 95% CI −0.22 to 0.42; 64 participants; 1 study; I^2 not applicable) (Analysis 1.3). The trial by López-Cedrún 2011 did not report SD, thus it could not be included into meta-analysis; however, the authors reported that VAS pain in the antibiotic group was significantly lower than in the placebo group.

Pre- and postoperative prophylaxis

Three trials evaluated the pain VAS score in this subgroup (Arteagoitia 2015; Barclay 1987; Kaczmarzyk 2007). These trials reported a protective role of antibiotics against pain (MD −0.75, 95% CI −1.22 to −0.28; 252 participants; 3 studies; I^2 = 0%) (Analysis 1.3).

Fever (sixth to seventh day)

Six trials reported fever as an outcome (Bystedt 1981; Happonen 1990; Lacasa 2007; López-Cedrún 2011; Milani 2015; Pasupathy 2011).

López-Cedrún 2011 and Pasupathy 2011 reported fever data in a way that did not permit inclusion in the meta-analysis.

The overall pooled estimate from the four parallel-arm RCTs that reported the outcome related to fever at day 6 or 7 showed no differences between the group who underwent antibiotic prophylaxis and the placebo group (RR 0.66, 95% CI 0.24 to 1.79; 475 participants; 4 studies; I^2 not applicable) (Analysis 1.4) (Bystedt 1981; Happonen 1990; Lacasa 2007; Milani 2015). Notably, only one trial recorded episodes of fever amongst participants (Happonen 1990). The rate of fever episodes in the antibiotic group was 2.4% (8/328), whilst the rate in the placebo group was 4.1% (6/147) (Table 5).

Preoperative prophylaxis

Only two trials employing preoperative prophylaxis reported the outcome related to fever, with no cases recorded in either study arm (Lacasa 2007; Milani 2015).

Postoperative prophylaxis

Three trials employing postoperative prophylaxis reported the outcome related to fever in this subgroup (Bystedt 1981; Happonen 1990; Lacasa 2007), but two of them did not record cases in either study arm (Bystedt 1981; Lacasa 2007). Only one trial recorded cases of participants with fever in both arms, with no significant differences between the antibiotic and placebo groups (RR 0.66, 95% CI 0.24 to 1.79; 296 participants; I^2 not applicable) (Analysis 1.4) (Happonen 1990).

Pre- and postoperative prophylaxis

Only one study employing pre- and postoperative prophylaxis reported data on fever, and recorded no cases in either group (Milani 2015).

Swelling day 7

Six trials reported swelling as an outcome (Arteagoitia 2015; Bystedt 1981; Kaczmarzyk 2007; Lacasa 2007; López-Cedrún 2011; Sekhar 2001).

We did not include Bystedt 1981 (pre- and postoperative prophylaxis) in meta-analysis because the outcome was reported in a graph, or Lacasa 2007 (preoperative prophylaxis, pre- and postoperative prophylaxis), which reported the value without SD.

The overall pooled estimate from the four parallel-arm trials that reported the outcome of swelling showed no differences between the group who underwent antibiotic prophylaxis and the placebo group (RR 0.80, 95% CI 0.50 to 1.27; 452 participants; 4 studies; I^2 = 44%) (Analysis 1.5) (Arteagoitia 2015; Kaczmarzyk 2007; López-

Cedrún 2011; Sekhar 2001). Overall heterogeneity was moderate, ranging from absent to substantial in the subgroups, whilst the test for subgroups differences was absent. The rate of swelling at day 7 was 25.3% (74/293) in the antibiotic group and 29.6% (47/159) the placebo group (Table 6).

Preoperative prophylaxis

Three trials employing preoperative prophylaxis reported the results related to swelling on the seventh day after surgery (Kaczmarzyk 2007; López-Cedrún 2011; Sekhar 2001). There was no statistical difference between the antibiotic and placebo groups (RR 1.13, 95% CI 0.69 to 1.83; 165 participants; 3 studies; $I^2 = 0\%$). Heterogeneity was absent (Analysis 1.5).

Postoperative prophylaxis

Two trials employing postoperative prophylaxis reported this outcome in this subgroup (López-Cedrún 2011; Sekhar 2001), with no difference between the antibiotics and placebo groups (RR 0.68, 95% CI 0.35 to 1.34; 128 participants; 2 studies; $I^2 = 35\%$). Heterogeneity was probably not important (Analysis 1.5).

Pre- and postoperative prophylaxis

Two trials employing pre- and postoperative prophylaxis reported this outcome (Arteagoitia 2015; Kaczmarzyk 2007), with no difference between the antibiotics and placebo groups (RR 0.54, 95% CI 0.10 to 2.98; 159 participants; 2 studies; $I^2 = 73\%$). Heterogeneity was substantial (Analysis 1.5).

Trismus (dichotomous) day 7

Seven studies investigated trismus amongst outcomes (Bortoluzzi 2013; Bystedt 1981; Happonen 1990; Kaczmarzyk 2007; Lacasa 2007; Milani 2015; Pasupathy 2011).

Four studies that provided data unsuitable for quantitative analysis were not included in the meta-analysis (Bystedt 1981; Happonen 1990; Lacasa 2007; Milani 2015). The overall pooled estimate from the three parallel-arm trials that reported the outcome of trismus showed no differences between the antibiotics and placebo groups (RR 0.77, 95% CI 0.42 to 1.41; 199 participants; 3 studies; $I^2 = 0\%$) (Analysis 1.6) (Bortoluzzi 2013; Kaczmarzyk 2007; Pasupathy 2011). Heterogeneity was absent in the overall meta-analysis, and the test for subgroups differences was not significant. The rate of trismus at day 6 to 7 was 16.0% (21/131) in the antibiotic group and 22.1% (15/68) in the placebo group (Table 7).

Preoperative prophylaxis

Three trials employing preoperative prophylaxis evaluated trismus at day 6 to 7 (Bortoluzzi 2013; Kaczmarzyk 2007; Pasupathy 2011), finding no evidence of a benefit of antibiotic prophylaxis (RR 0.73, 95% CI 0.36 to 1.46; 158 participants; 3 studies; $I^2 = 0\%$; Analysis 1.6).

Postoperative prophylaxis

No trials employing postoperative prophylaxis reported trismus.

Pre- and postoperative prophylaxis

Only one trial employing pre- and postoperative prophylaxis evaluated trismus (Kaczmarzyk 2007), finding no evidence of a difference between antibiotic and placebo (RR 0.93, 95% CI 0.27 to 3.14; 41 participants; Analysis 1.6).

Dry socket

Fourteen trials reported the outcome of dry socket: 13 parallel-arm RCTs (Arteagoitia 2005; Arteagoitia 2015; Barclay 1987; Bergdahl 2004; Bortoluzzi 2013; Bystedt 1980; Bystedt 1981; Gbotolorun 2016; Halpern 2007; Kaczmarzyk 2007; López-Cedrún 2011; Pasupathy 2011; Ritzau 1992), and one split-mouth cross-over RCT (Bezerra 2011).

The pooled estimate for all 13 parallel-arm trials that reported on dry socket was RR 0.66 (95% CI 0.45 to 0.97; 1882 participants; 13 studies; $I^2 = 0\%$; Analysis 1.7). Overall heterogeneity was absent, as was heterogeneity between subgroups. The postoperative prophylaxis group showed moderate heterogeneity. The rate of infections ranged from 0 to 56% in the placebo group and 0 to 16% in the antibiotic group. There was a reduction in the risk of infection from a mean of 6.3% (56/890) in the placebo group to 3.8% (40/1060) in the antibiotic group (Table 8).

Preoperative prophylaxis

Eight trials employing preoperative prophylaxis reported this outcome: seven parallel-arm RCTs (Bergdahl 2004; Bortoluzzi 2013; Halpern 2007; Kaczmarzyk 2007; López-Cedrún 2011; Pasupathy 2011; Ritzau 1992), and one split-mouth cross-over RCT (Bezerra 2011). Three trials did not record any dry socket in either group (Halpern 2007; López-Cedrún 2011; Pasupathy 2011). The pooled estimate showed no evidence of benefit for preoperative antibiotics (RR 0.75, 95% CI 0.42 to 1.34; 724 participants; 7 studies; $I^2 = 0\%$). Heterogeneity was absent (Analysis 1.7).

The study with a split-mouth cross-over design reported an equal number of dry sockets in the two groups (1/34 antibiotic versus 1/34 placebo) (Bezerra 2011).

Postoperative prophylaxis

Three trials employing postoperative prophylaxis reported the outcome of dry socket. The trial by López-Cedrún 2011 did not detect any dry socket in either group, whilst the remaining trials showed no difference between antibiotic and placebo groups (RR 0.82, 95% CI 0.12 to 5.54; 704 participants; 3 studies; $I^2 = 41\%$) (Arteagoitia 2005; Gbotolorun 2016). Heterogeneity was moderate (Analysis 1.7).

Pre- and postoperative prophylaxis

Five trials employing pre- and postoperative prophylaxis reported dry socket (Arteagoitia 2015; Barclay 1987; Bystedt 1980; Bystedt 1981; Kaczmarzyk 2007). The pooled estimate showed a reduction in the risk of dry socket among those taking postoperative prophylaxis (RR 0.50, 95% CI 0.28 to 0.90; 454 participants; 5 studies; $I^2 = 0\%$). Heterogeneity was absent (Analysis 1.7).

Adverse effects

The overall pooled estimate from the eight parallel-arm trials that reported the outcome of side effects showed no differences between the group who underwent antibiotic prophylaxis and the placebo group (RR 1.46, 95% CI 0.81 to 2.64; 1277 participants; 8 studies; $I^2 = 53\%$; Analysis 1.8). Heterogeneity was moderate, whilst the heterogeneity for subgroup differences was not important ($I^2 = 18.8\%$; P = 0.29). Heterogeneity could be explained by how different authors diagnosed relevant side effects. Indeed, the two studies from the same author demonstrated a significant difference

between groups, with side effects more prevalent in the antibiotic group (Arteagoitia 2005; Arteagoitia 2015). The rate of side effects was 10.3% (78/756) in the antibiotic group and 6.9% (36/521) in the placebo group (Table 9); the nature of the side effects included diarrhoea, abdominal pain, and others (Table 10).

Preoperative prophylaxis

Five trials employing preoperative prophylaxis reported the incidence of adverse effects (Bystedt 1981; Kaczmarzyk 2007; Lacasa 2007; López-Cedrún 2011; Milani 2015). Three of these studies reported no episodes of side effects in either the antibiotic and placebo group (Bystedt 1981; Kaczmarzyk 2007; Milani 2015), whilst the other two trials did not show significant differences between groups (RR 0.96, 95% CI 0.49 to 1.90; 317 participants; 5 studies; I^2 = 0%). There was no heterogeneity (Analysis 1.8).

Postoperative prophylaxis

Three trials employing postoperative prophylaxis reported this outcome (Arteagoitia 2005; Lacasa 2007; López-Cedrún 2011). There was no significant difference between groups (RR 1.26, 95% CI 0.24 to 6.51; 666 participants; 3 studies; I^2 = 77%). Heterogeneity was substantial, and it should be highlighted that the trial by Arteagoitia 2005, which had the largest sample, reported a significant prevalence of side effects in the antibiotic group (Analysis 1.8).

Pre- and postoperative prophylaxis

Four trials employing pre- and postoperative prophylaxis reported this outcome (Arteagoitia 2015; Barclay 1987; Kaczmarzyk 2007; Milani 2015). Milani 2015 reported no adverse effects in either group. There was no significant difference between the antibiotic and placebo group (RR 2.44, 95% CI 0.95 to 6.24; 294 participants; 4 studies; I^2 = 36%). Heterogeneity was not important. Arteagoitia 2015 was the only trial that showed a significant difference between groups, with side effects more prevalent in the antibiotic group (Analysis 1.8).

DISCUSSION

Summary of main results

We included 23 double-blind, placebo-controlled trials with more than 3206 participants (2583 analysed) in the review. Participants in 21 studies underwent extraction of third molar (wisdom) teeth; participants in one study underwent routine intra-alveolar extraction; and one study enrolled patients who needed complex oral surgery with an estimated intervention length of less than 90 minutes, including avulsion with alveolectomy, avulsion of a tooth under mucous membrane, avulsion of impacted tooth, or multiple avulsions (> 3 teeth). None of the included studies were of patients undergoing tooth extraction in general dental practice, for the removal of severely decayed teeth; even the study focused on intra-alveolar extractions included patients from the dental outpatient department of a general hospital.

Sixteen of the included trials were at high risk of bias, four were at unclear risk of bias, and the remaining three were at low risk of bias.

Antibiotics, administered to prevent infection in patients undergoing wisdom tooth extraction, may reduce the risk of infection by approximately 66% (low-certainty evidence) (Summary of findings 1). We found no clear evidence that the timing

of antibiotic administration (preoperative, postoperative, or both) was important.

There may be no difference between antibiotics and placebo for the outcomes of pain (whether measured dichotomously or continuously), fever, swelling, or trismus seven days after tooth extraction (very low-certainty evidence).

Whilst antibiotic prophylaxis seems to reduce the risk of infection and dry socket, these outcomes still occur in some healthy people who take antibiotic prophylaxis associated with the extraction of impacted third molars. It is interesting to note that the rate of infection in the placebo groups in the included trials varied between zero, Bortoluzzi 2013; Gbotolorun 2016; Leon Arcila 2001; Sekhar 2001, and 56%, Mitchell 1986, with a mean of 8.5% across the placebo groups of the included studies (Table 2). Based on the evidence presented in this review, the use of prophylactic antibiotics may reduce infection to a mean of 2.6%, which means that approximately 19 (95% CI 15 to 34) people would need to receive antibiotic prophylaxis to prevent one infection.

The incidence of dry socket in the placebo group varied between zero, Arteagoitia 2015; Halpern 2007; López-Cedrún 2011; Pasupathy 2011, and 34%, Barclay 1987, with a mean of 6.3%. This means that approximately 46 (95% CI 29 to 521) healthy people would need to be treated with prophylactic antibiotics to prevent one case of dry socket (Table 8).

Using prophylactic antibiotics might result in at least one adverse event for every 32 people treated (9 to 77 number needed to treat for an additional harmful outcome), though adverse effects reported in the trials were generally mild and transient.

Overall completeness and applicability of evidence

We conducted a comprehensive search including both electronic and handsearching through reference lists. We identified 23 randomised, double-blind, placebo-controlled trials that involved a combined total of approximately 2600 (analysed) participants. All but one trial included healthy patients in their 20s who were undergoing extraction of impacted teeth (mainly of the lower jaw), thus making the results of our review sound in regards to the effectiveness of antibiotic prophylaxis of infectious complications in healthy young people undergoing wisdom tooth extractions, which is a very large proportion of surgical tooth extractions. However, we identified no trials of patients attending general dental practices for tooth extraction due to caries or periodontitis; in one trial, most of patients attending the dental outpatient department of a general hospital had extraction mainly due to caries or periodontitis (Gbotolorun 2016). The identified trials did not include patients with depressed immune systems, patients with other illnesses, young children, or elderly people. Indeed, it is unlikely to be feasible or ethical to conduct placebo-controlled trials in this group of patients. The results of this review may or may not be generalisable to this group, who would be expected to be at higher risk of infection. However, extrapolating from the results of this review, it may be that in people at higher risk of infectious complications, antibiotic prophylaxis may be more effective, with a lower 'number needed to treat' with antibiotics in order to prevent one infection; this is particularly important given that in such patients, an infective complication can have more serious consequences due to the impaired ability of the immune system to avoid spreading of the infection.

Another limit to generalisability of our results regards the clinical skill of the operators, who in the included studies were mainly oral surgery specialists working in referral centres. Whether results would be similar for general dental practitioners is unclear.

Adverse event frequency and severity can be important determinants in deciding whether to administer a preventive treatment. As is the case for many medical areas, the quality and quantity of information about adverse effects of interventions in these trials was inadequate (Ioannidis 2009). However, based on dropout rates and the adverse effects in the eight trials that reported the frequency of adverse effects per participant, it seems likely that adverse effects were generally mild and well tolerated.

We could not draw any conclusions on the extent to which the use of prophylactic antibiotics in association with tooth extraction in healthy people may affect the subsequent development of strains of bacteria resistant to antibiotics in common use in these situations (EU Commission 2011; EU Commission 2019).

Quality of the evidence

Although this review was restricted to double-blind, placebo-controlled trials, only three of the included trials were at low risk of bias overall (four trials were at unclear risk and 16 were at high risk of bias). The most common sources of bias were missing outcome data and selective reporting. In trials such as many of those included in this review, where the outcome events are uncommon even in the placebo group, losses to follow-up can potentially result in misleading results.

We evaluated the certainty of the body of evidence included in this review using the GRADE approach (see Summary of findings 1). The certainty of the evidence was very low for most outcomes due to high or unclear risk of bias, confidence intervals that crossed the line of no effect, and heterogeneity between studies. We graded the certainty of the evidence for the outcomes postsurgical infectious complications and dry socket as low due to high risk of bias. We downgraded the evidence for indirectness, as most of the trials were performed only in healthy patients undergoing wisdom tooth extractions.

The evidence concerning the use of prophylactic antibiotics in patients undergoing extraction for severe caries or periodontitis came from a single study (Gbotolorun 2016).

Potential biases in the review process

Data from some of the studies included in the current review, namely the older ones, could not be entered in the meta-analysis due to poor reporting, which prevented data extraction. This may have introduced reporting bias into the review. The funnel plots for the primary outcome of postsurgical infectious complications (Figure 4) and secondary outcome dry socket (Figure 5) showed no evidence of publication bias (note that the points on the plot are not independent because three of the trials are included in two subgroups (Kaczmarzyk 2007; Lacasa 2007; López-Cedrún 2011)).

Figure 4. Funnel plot of comparison: antibiotic versus placebo, outcome: infectious complications.
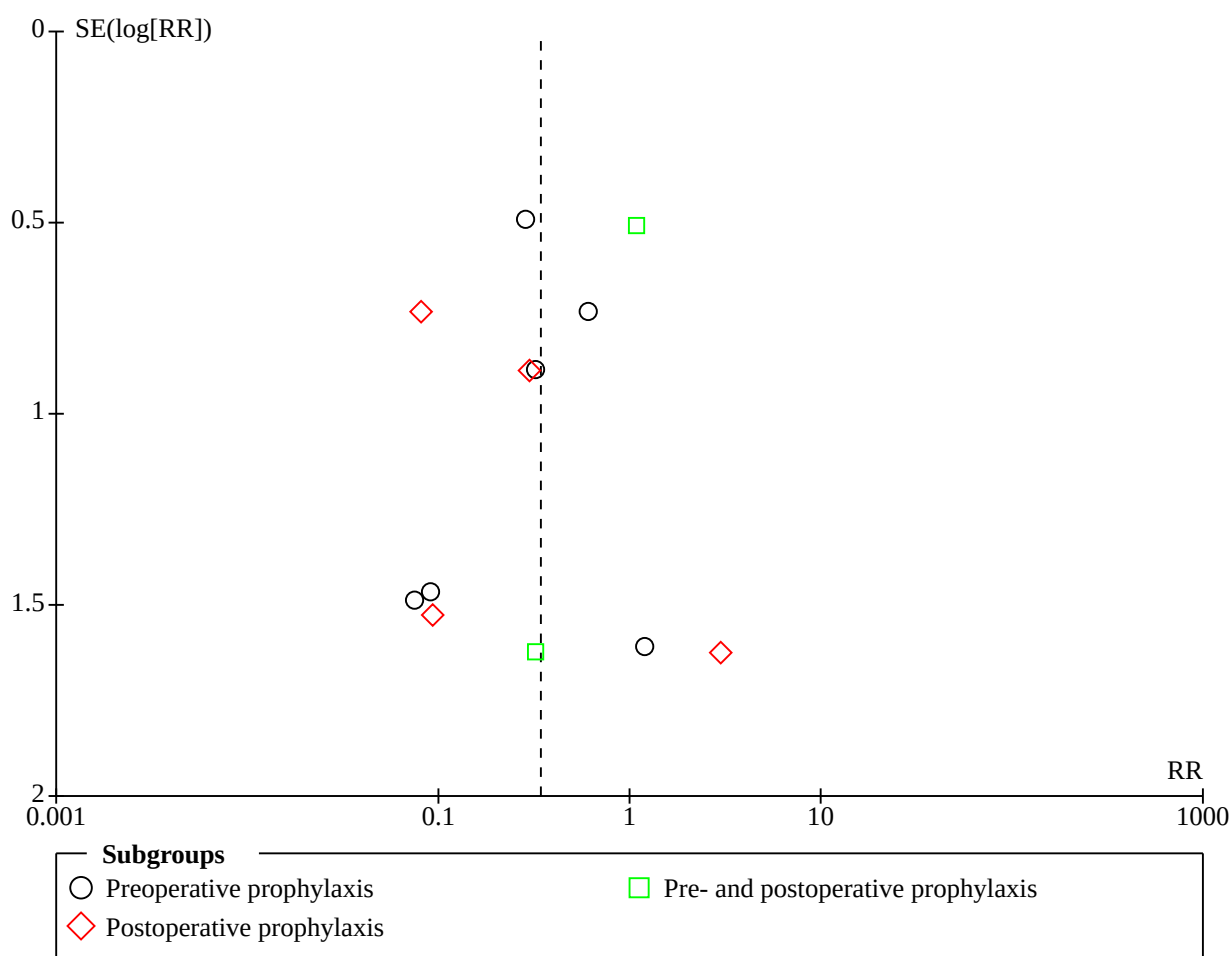
Figure 5. Funnel plot of comparison: antibiotic versus placebo, outcome: dry socket.
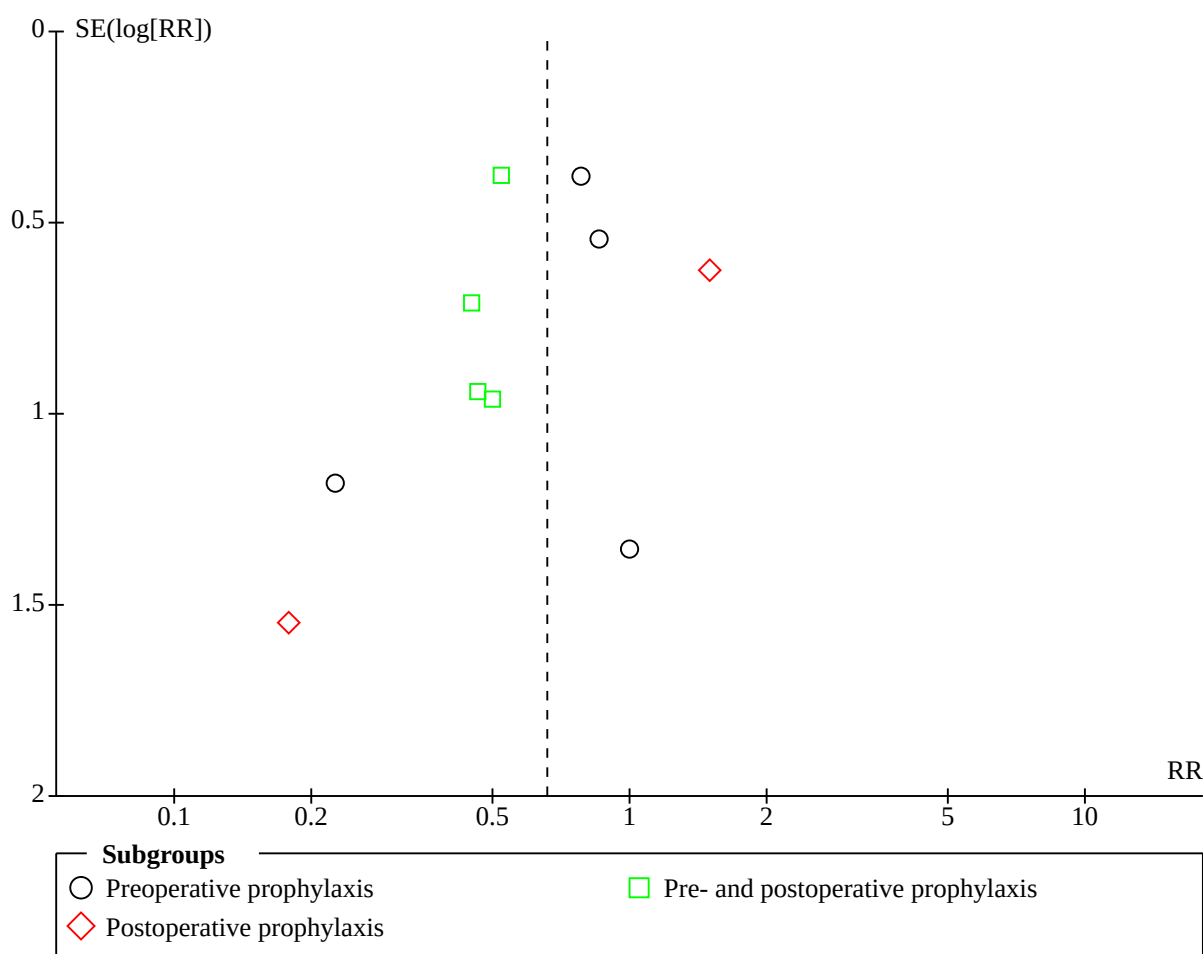
In the protocol for this review, we planned to only include trials where the important clinical outcome of infection was reported. In this update, we made it more explicit that we excluded trials that only reported other or intermediate outcomes (endocarditis incidence, bacteraemia, or serum marker of infection). We consider that these changes have resulted in higher quality, clinically relevant trials being included in the review.

Agreements and disagreements with other studies or reviews

A previous review in 2007 included a different group of studies due to the use of different inclusion criteria, which considered mandibular third molar extractions only and did not limit the review to double-blind studies. Ren 2007 concluded that antibiotic administration was effective in preventing wound infection, although they reported a higher number needed to treat for an additional harmful outcome: "on average 25 patients needed to be treated with systemic antibiotics to prevent 1 case of extraction wound infection" in this group of healthy patients.

More recently, several other systematic reviews and meta-analyses have assessed studies focused on third molar surgery (thus with different inclusion criteria than the current review),

and they also focused on a specific antibiotic molecule. Three meta-analyses focused on the use of amoxicillin, finding that it does not reduce the risk of infection or dry socket (or both) after third molar extraction (Arteagoitia 2016; Isiordia-Espinoza 2015; Menon 2019). Conversely, the association of amoxicillin/clavulanic acid seems to be effective (Arteagoitia 2016; Menon 2019). Nevertheless, Arteagoitia 2016 did not support the routine prescription of antibiotic due the number needed to treat for an additional beneficial outcome, the low prevalence of infection, the potential adverse reactions to antibiotics, and the lack of serious complications in placebo groups.

A couple of meta-analyses reported discordant results about the effectiveness of nitromimidazoles to reduce the risk of dry socket or infection (or both) in third molar extraction (Isiordia-Espinoza 2018; Ramos 2016).

AUTHORS' CONCLUSIONS

Implications for practice

Most of the literature shed light on a subset of patients undergoing dental extractions: healthy people who had surgical extraction of third molars. There is low-certainty evidence that in this subset of patients, the use of prophylactic antibiotics reduces the risk

of infectious complications. We found no clear evidence that the timing of antibiotic administration (preoperative, postoperative, or both) is important. On average, treating 19 healthy patients with prophylactic antibiotics may prevent one infection. Consequently, when deciding whether to use antibiotic prophylaxis to prevent infective complications following tooth extractions in healthy patients, the practitioner should consider the possible increased risk of mild adverse effects (at least one for every 30 people treated), the low rate of infectious complications (approximately 40 people treated to prevent one case of dry socket), and the lack of serious complications even in the absence of antibiotic prophylaxis. Another important aspect of reconsidering the routine prescription of antibiotic prophylaxis is the growing emphasis on limiting the use of antibiotics in order to stop increasing microbial resistance to drugs. Evidence is lacking about the effects of prophylactic antibiotics in patients with concomitant illnesses or patients at a higher risk of infection.

Implications for research

The evidence for the effectiveness of antibiotic prophylaxis in preventing infectious complications cannot be generalised to either non-healthy patients or less invasive intra-alveolar extraction lacking alveolectomy. Future trials should investigate prophylactic antibiotics effectiveness in patients at high risk of infective complications, such as immunocompromised people and people who have experienced infective complications following previous extractions, although undertaking research in these groups of people may not be possible or ethical. Conversely, the single trial investigating intra-alveolar extractions for severe caries or periodontal disease in healthy patients failed to find any significant role for antibiotic prophylaxis in preventing infectious complications. Future studies should also measure the outcomes of symptoms and clinical assessment using standardised measures and time points, and report these according to CONSORT guidelines.

ACKNOWLEDGEMENTS

REFERENCES

References to studies included in this review

Arteagoitia 2005 *{published data only}*

Arteagoitia I, Diez A, Barbier L, Santamaria G, Santamaria J. Efficacy of amoxicillin/clavulanic acid in preventing infectious and inflammatory complications following impacted mandibular third molar extraction. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 2005;**100**(1):e11-8.

Arteagoitia 2015 *{published data only}*

Arteagoitia I, Ramos E, Santamaria G, Barbier L, Alvarez J, Santamaria J. Amoxicillin/clavulanic acid 2000/125 mg to prevent complications due to infection following completely bone-impacted lower third molar removal: a clinical trial. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 2015;**119**:8-16.

Barclay 1987 *{published data only}*

Barclay JK. Metronidazole and dry socket: prophylactic use in mandibular third molar removal complicated by non-acute pericoronitis. *New Zealand Dental Journal* 1987;**83**:71-5.

Bergdahl 2004 *{published data only}*

Bergdahl M, Hedstrom L. Metronidazole for the prevention of dry socket after removal of partially impacted mandibular third molar: a randomised controlled trial. *British Journal of Oral & Maxillofacial Surgery* 2004;**42**(6):555-8.

Bezerra 2011 *{published and unpublished data}*

Bezerra T. Poster Board Number: 16: Prophylaxis versus placebo treatment for infective and inflammatory complications of surgical third molar removal: a split-mouth, double-blind, controlled, clinical trial with amoxicillin (500 mg). *Journal of Oral and Maxillofacial Surgery* 2010;**68**(9 (Suppl)):e69.

*

ZZZ <label> ZZZ*

Bezerra TP, Studart-Soares EC, Scaparo HC, Pita-Neto IC, Batista SH, Fonteles CS. Prophylaxis versus placebo treatment for infective and inflammatory complications of surgical third molar removal: a split-mouth, double-blind, controlled, clinical trial with amoxicillin (500 mg). *Journal of Oral & Maxillofacial Surgery* 2011;**69**(11):e333-9.

Bortoluzzi 2013 *{published data only}*

Bortoluzzi MC, Capella DL, Barbieri T, Pagliarini M, Cavalieri T, Manfro R. A single dose of amoxicillin and dexamethasone for prevention of postoperative complications in third molar surgery: a randomized, double-blind, placebo controlled clinical trial. *Journal of Clinical Medicine Research* 2013;**5**:26-33.

Bystedt 1980 *{published data only}*

Bystedt H, Nord CE, Nordenram A. Effect of azidocillin, erythromycin, clindamycin and doxycycline on postoperative complications after surgical removal of impacted mandibular third molars. International Journal of Oral Surgery 1980;**9**(3):157-65.

Bystedt 1981 *{published data only}*

Bystedt H, von Konow L, Nord CE. A comparison of the effect of phenoxymethylpenicillin and azidocillin on postoperative complications after surgical removal of impacted mandibular third molars. *Swedish Dental Journal* 1981;**5**(5-6):225-34.

Gbotolorun 2016 *{published data only}*

Gbotolorun OM, Dipo-Fagbemi IM, Olojede AO, Ebigwei S, Adetoye JO. Are systemic antibiotics necessary in the prevention of wound healing complications after intra-alveolar dental extraction? *International Journal of Oral and Maxillofacial Surgery* 2016;**45**:1658-64.

Halpern 2007 *{published data only}*

Halpern LR, Dodson TB. Does prophylactic administration of systemic antibiotics prevent postoperative inflammatory complications after third molar surgery? *Journal of Oral and Maxillofacial Surgery* 2007;**65**(2):177-85.

Happonen 1990 *{published data only}*

Happonen RP, Backstrom AC, Ylipaavalniemi P. Prophylactic use of phenoxymethylpenicillin and tinidazole in mandibular third molar surgery, a comparative placebo controlled clinical trial. *British Journal of Oral & Maxillofacial Surgery* 1990;**28**(1):12-5.

Kaczmarzyk 2007 *{published data only}*

Kaczmarzyk T, Wichlinski J, Stypulkowska J, Zaleska M, Panas M, Woron J. Single-dose and multi-dose clindamycin therapy fails to demonstrate efficacy in preventing infectious and inflammatory complications in third molar surgery. *International Journal of Oral and Maxillofacial Surgery* 2007;**36**(5):417-22.

Kaziro 1984 *{published data only}*

Kaziro GS, Harris M. A comparative placebo controlled trial between metronidazole and Arnica Montana in preventing post-surgical complications. *Journal of Dental Research* 1981;**60**(Special Issue):1176.

*

ZZZ <label> ZZZ*

Kaziro GS. Metronidazole (Flagyl) and Arnica Montana in the prevention of post-surgical complications, a comparative placebo controlled clinical trial. *British Journal of Oral & Maxillofacial Surgery* 1984;**22**(1):42-9.

Lacasa 2007 *{published data only}*

Lacasa JM, Jiménez JA, Ferrás V, Bossom M, Sóla-Morales O, García-Rey C, et al. Prophylaxis versus pre-emptive treatment for infective and inflammatory complications of surgical third molar removal: a randomized, double-blind, placebo-controlled, clinical trial with sustained release amoxicillin/clavulanic acid (1000/62.5 mg). *International Journal of Oral and Maxillofacial Surgery* 2007;**36**(4):321-7.

Leon Arcila 2001 *{published and unpublished data}*

Leon Arcila ME, Acosta P, Bravo BE, Mena A, Noguera DP, Zúñiga JR. Antibiotic prophylaxis in third molar surgery

[Profilaxis antibiotica en cirugia de terceros molares incluidos]. Revista Estomatologia 2001;**9**(2):4-13.

López-Cedrún 2011 *{published and unpublished data}*

López-Cedrún JL, Pijoan JI, Fernández S, Santamaria J, Hernandez G. Efficacy of amoxicillin treatment in preventing postoperative complications in patients undergoing third molar surgery: a prospective, randomized, double-blind controlled study. *Journal of Oral and Maxillofacial Surgery* 2011;**69**:e5-14.

MacGregor 1980 *{published data only}*

*

ZZZ <label> ZZZ*
MacGregor AJ, Addy A. Value of penicillin in the prevention of pain, swelling and trismus following the removal of ectopic mandibular third molars. *International Journal of Oral Surgery* 1980;**9**(3):166-72.

MacGregor AJ, Addy AG. The effect of penicillin upon pain, swelling and trismus following the removal of impacted third molars. *Journal of Dental Research* 1980;**59**(Special Issue D Part 1):1799 (Abs No 35).

Milani 2015 *{published data only}*

Milani BA, Bauer HC, Sampaio-Filho H, Horliana AC, Perez FE, Tortamano IP, et al. Antibiotic therapy in fully impacted lower third molar surgery: randomized three-arm, double-blind, controlled trial. *Oral and Maxillofacial Surgery* 2015;**19**:341-6.

Mitchell 1986 *{published data only}*

Mitchell DA. A controlled clinical trial of prophylactic tinidazole for chemoprophylaxis in third molar surgery. *British Dental Journal* 1986;**160**(8):284-6.

Pasupathy 2011 *{published data only}*

Pasupathy S, Alexander M. Antibiotic prophylaxis in third molar surgery. *Journal of Craniofacial Surgery* 2011;**22**:551-3.

Ritzau 1992 *{published data only}*

Ritzau M, Hillerup S, Branebjerg PE, Ersbol BK. Does metronidazole prevent alveolitis sicca dolorosa? A double-blind, placebo-controlled clinical study. *International Journal of Oral and Maxillofacial Surgery* 1992;**21**(5):299-302.

Sekhar 2001 *{published data only}*

Sekhar CH, Narayanan V, Baig MF. Role of antimicrobials in third molar surgery: prospective, double blind, randomized, placebo-controlled clinical study. British Journal of Oral & Maxillofacial Surgery 2001;**39**(2):134-7.

Sixou 2012 *{published data only}*

Sixou M, Burban J, Lakhssassi N, Duran D, De Mello G, Quéro J. Amoxicillin prophylaxis in oral surgery. *Revue de Stomatologie et Chirurgie Maxillo-Faciale* 2012;**113**:358-64.

References to studies excluded from this review

Abu-Mowais 1990 *{published data only}*

Abu-Mowais M, Abdul-Amir R, El-Mostehy MR, Mansour M, Mohalhal I. The clinical safety and efficacy of antibiotic prophylaxis after surgical removal of third molars. Journal of the Kuwait Medical Association 1990;**24**(1):57-9.

Adde 2012 *{published data only}* 10.1016/j.tripleo.2011.08.018

Adde CA, Soares MS, Romano MM, Carnaval TG, Sampaio RM, Aldarvis FP, et al. Clinical and surgical evaluation of the indication of postoperative antibiotic prescription in third molar surgery. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 2012;**114**:S26-31. [DOI: 10.1016/j.tripleo.2011.08.018]

Arora 2014 *{published data only}* 10.4103/0975-5950.154821

Arora A, Roychoudhury A, Bhutia O, Pandey S, Singh S, Das BK. Antibiotics in third molar extraction; are they really necessary: a non-inferiority randomized controlled trial. *National Journal of Maxillofacial Surgery* 2014;**5**:166-71. [DOI: 10.4103/0975-5950.154821]

Ataoglu 2008 *{published data only}*

Ataoğlu H, Oz GY, Candirli C, Kiziloğlu D. Routine antibiotic prophylaxis is not necessary during operations to remove third molars. *British Journal of Oral & Maxillofacial Surgery* 2008;**46**(2):133-5.

Bargnesi 1985 *{published data only}*

Bargnesi R, Bondi C, Cavalli A, Vallania G. A clinical double blind study of the usefulness of systemic prophylactic antibiotic therapy in minor oral surgery. *Giornale di Stomatologia e di Ortognatodonzia* 1985;**4**(2):29-32.

Barone 2017 *{published and unpublished data}*

Barone A, Marchionni FS, Cinquini C, Cipolli Panattoni A, Toti P, Marconcini S, et al. Antibiotic treatment to prevent postextraction complications: a monocentric, randomized clinical trial. Preliminary outcomes. *Minerva Stomatologica* 2017;**66(4)**:148-56.

*

ZZZ <label> ZZZ*
Marchionni FS. Antibiotic treatment to prevent postextraction complications: a monocentric, randomized clinical trial. Preliminary outcomes [PhD thesis]. Pisa (Italy): Università di Pisa, 2017.

Busa 2014 *{published data only}* 10.1097/SCS.0000000000000431

Busa A, Parrini S, Chisci G, Pozzi T, Burgassi S, Capuano A. Local versus systemic antibiotics effectiveness: a comparative study of postoperative oral disability in lower third molar surgery. *Journal of Craniofacial Surgery* 2014;**25**:708-9. [DOI: 10.1097/SCS.0000000000000431]

Curran 1974 *{published data only}*

Curran JB, Kennett S, Young AR. An assessment of the use of prophylactic antibiotics in third molar surgery. International Journal of Oral Surgery 1974;**3**(1):1-6.

Delilbasi 2004 *{published data only}*

Delilbasi C, Saracoglu U, Keskin A. Effects of 0.2% chlorhexidine gluconate and amoxicillin plus clavulanic acid on the prevention of alveolar osteitis following mandibular third molar extractions. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, & Endodontology* 2002;**94**(3):301-4.

de Moura 2011 *{published data only}*

de Moura WL, Freire SASR, Mendes SM, Olate S. Efficacy of amoxicillin treatment in preventing postoperative complications in patients undergoing third molar surgery: a double blind study [Eficacia del tratamiento con amoxicilina en la prevención de complicaciones postoperatorias en pacientes sometidos a cirugía del tercer molar: un estudio doble ciego]. *International Journal of Odontostomatology* 2011;**5**(2):147-52.

Foy 2004 *{published data only}*

Foy SP, Shugars DA, Phillips C, Marciani RD, Conrad SM, White RP Jr. The impact of intravenous antibiotics on health-related quality of life outcomes and clinical recovery after third molar surgery. *Journal of Oral and Maxillofacial Surgery* 2004;**62**(1):15-21.

Fridrich 1990 *{published data only}*

Fridrich KL, Olson RA. Alveolar osteitis following surgical removal of mandibular third molars. *Anesthesia Progress* 1990;**37**(1):32-41.

Graziani 2005 *{published data only}*

Graziani F, Corsi L, Fornai M, Antonioli L, Tonelli M, Ceia S, et al. Clinical evaluation of piroxicam-FDDF and azithromycin in the prevention of complications associated with impacted lower third molar extraction. *Pharmacological Research* 2005;**52**(6):485-90.

Grossi 2007 *{published data only}*

Grossi GB, Maiorana C, Garramone RA, Borgonovo A, Creminelli L, Santoro F. Assessing postoperative discomfort after third molar surgery: a prospective study. *Journal of Oral and Maxillofacial Surgery* 2007;**65**(5):901-17.

Head 1984 *{published data only}*

Head TW, Bentley KC, Millar EP, deVries JA. A comparative study of the effectiveness of metronidazole and penicillin V in eliminating anaerobes from postextraction bacteremias. *Oral Surgery, Oral Medicine, and Oral Pathology* 1984;**58**(2):152-5.

Krekmanov 1980 *{published data only}*

Krekmanov L, Hallander HO. Relationship between bacterial contamination and alveolitis after third molar surgery. *International Journal of Oral Surgery* 1980;**9**(4):274-80.

Krekmanov 1981 *{published data only}*

Krekmanov L. Alveolitis after operative removal of third molars in the mandible. *International Journal of Oral Surgery* 1981;**10**(3):173-9.

Krekmanov 1986 *{published data only}*

Krekmanov L, Nordenram A. Postoperative complications after surgical removal of mandibular third molars. Effects of penicillin V and chlorhexidine. *International Journal of Oral and Maxillofacial Surgery* 1986;**15**(1):25-9.

Laird 1972 *{published data only}*

Laird WR, Stenhouse D, Macfarlane TW. Control of postoperative infection. A comparative evaluation of clindamycin and phenoxymethylpenicillin. British Dental Journal 1972;**133**(3):106-9.

Limeres 2009 *{published data only}*

Limeres J, Sanromán JF, Tomás I, Diz P. Patients' perception of recovery after third molar surgery following postoperative treatment with moxifloxacin versus amoxicillin and clavulanic acid: a randomized, double-blind, controlled study. *Journal of Oral and Maxillofacial Surgery* 2009;**67**(2):286-91.

Lombardia Garcia 1987 *{published data only}*

Lombardía García E, García Pola MJ, González García M, Gener González M. Antimicrobial prophylaxis in surgery of the third molar. Analytic study of postoperative complications. *Archivos de Odonto Estomatologia* 1987;**3**(3):130-4.

Lopes 2011 *{published data only}*

Lopes DR, Peres MP, Levin AS. Randomized study of surgical prophylaxis in immunocompromised hosts. *Journal of Dental Research* 2011;**90**(2):225-9.

Luaces-Rey 2010 *{published data only}*

Luaces-Rey R, Arenaz-Búa J, Lopez-Cedrun-Cembranos JL, Martínez-Roca C, Pértega-Díaz S, Sironvalle-Soliva S. Efficacy and safety comparison of two amoxicillin administration schedules after third molar removal. A randomized, double-blind and controlled clinical trial. *Medicina Oral, Patologia Oral y Cirugia Bucal* 2010;**15**(4):633-8.

Lyall 1991 *{published data only}*

Lyall JB. Third molar surgery: the effect of primary closure, wound dressing and metronidazole on postoperative recovery. *Journal of the Royal Army Medical Corps* 1991;**137**(2):100-3.

MacGregor 1973 *{published data only}*

MacGregor AJ, Hutchinson D. The effect of Nivemycin on pain and swelling following lower third molar removal. British Journal of Oral Surgery 1973;**10**(3):321-5.

Milani 2012 *{published data only}*

Milani BA, Jorge WA, Peixoto IF, Ratto Tempestini Horlana AC, Bauer HC. Clinical evaluation of the efficacy of Amoxiline given in multiple doses in the postoperative period of extraction of lower third molars [Avaliacao clinica da eficacia da Amoxilina ministrada em multiplas doses no pos-operatorio de exodontias de terceiros molares inferiores]. *RPG - Revista da Pós-Graduação* 2012;**19**:69-75.

Mitchell 1987 *{published data only}*

Mitchell DA, Morris TA. Tinidazole or pivampicillin in third molar surgery. *International Journal of Oral and Maxillofacial Surgery* 1987;**16**(2):171-4.

Monaco 1999 *{published data only}*

Monaco G, Staffolani C, Gatto MR, Checchi L. Antibiotic therapy in impacted third molar surgery. *European Journal of Oral Science* 1999;**6**(107):437-41.

Monaco 2009 *{published data only}*

Monaco G, Tavernese L, Agostini R, Marchetti C. Evaluation of antibiotic prophylaxis in reducing postoperative infection after mandibular third molar extraction in young patients. *Journal of Oral and Maxillofacial Surgery* 2009;**67**(7):1467-72.

Olusanya 2011 *{published data only}*

Olusanya AA, Arotiba JT, Fasola OA, Akadiri AO. Prophylaxis versus pre-emptive antibiotics in third molar surgery: a randomised control study. Nigerian Postgraduate Medical Journal 2011;**18**(2):105-10.

Osborn 1979 *{published data only}*

Osborn JF, Jaques WA, Thalmann R, Spiessl B. Efficiency of systemic prophylactic antibiotics in the surgical removal of lower wisdom teeth. *SSO: Schweizerische Monatsschrift fur Zahnheilkunde* 1979;**89**(5):458-66.

Poeschl 2004 *{published data only}*

*

ZZZ <label> ZZZ*

Poeschl PW, Eckel D, Poeschl E. Postoperative prophylactic antibiotic treatment in third molar surgery - a necessity? *Journal of Oral and Maxillofacial Surgery* 2004;**62**(1):3-9.

Poeschl PW, Eckel D. Antibiotic prophylaxis after out-patient removal of wisdom teeth: a necessity? *Stomatologie* 2003;**100**(5):115.

Reekie 2006 *{published data only}*

Reekie D, Downes P, Devlin CV, Nixon GM, Devlin H. The prevention of 'dry socket' with topical metronidazole in general dental practice. *British Dental Journal* 2006;**200**(4):210-3.

Rood 1979 *{published data only}*

Rood JP, Murgatroyd J. Metronidazole in the prevention of 'dry socket'. British Journal of Oral Surgery 1979;**17**(1):62-70.

Samsudin 1994 *{published data only}*

Samsudin AR, Mason DA. Symptoms from impacted wisdom teeth. *British Journal of Oral & Maxillofacial Surgery* 1994;**32**(6):380-3.

Siddiqi 2010 *{published data only}*

Siddiqi A, Morkel JA, Zafar S. Antibiotic prophylaxis in third molar surgery: a randomized double-blind placebo-controlled clinical trial using split-mouth technique. *International Journal of Oral and Maxillofacial Surgery* 2010;**39**(2):107-4.

Stavropoulos 2006 *{published data only}*

Stavropoulos MF, Shugars DA, Phillips C, Conrad SM, Fleuchaus PT, White RP Jr. Impact of topical minocycline with third molar surgery on clinical recovery and health-related quality of life outcomes. *Journal of Oral and Maxillofacial Surgery* 2006;**64**(7):1059-65.

Sulejmanagić 2005 *{published data only}*

Sulejmanagić N, Sulejmanagić H, Ljutović Z, Salihagić D, Sijercić M. Combined application of amoxicillin and clavulanic acid after oral surgical interventions. *Bosnian Journal of Basic Medical Science* 2005;**5**(1):61-8.

Swanson 1989 *{published data only}*

Swanson AE. A double-blind study on the effectiveness of tetracycline in reducing the incidence of fibrinolytic alveolitis. *Journal of Oral and Maxillofacial Surgery* 1989;**47**(2):165-7.

Uluibau 2005 *{published data only}*

Uluibau IC, Jaunay T, Goss AN. Severe odontogenic infections. *Australian Dental Journal* 2005;**50**(2):S74-81.

Walkow 1995 *{published data only}*

Walkow T, Papageorge M, Norris L, Cottrell D. Prophylactic antibiotic efficacy in third molar surgery (AADR Abstract 1995). *Journal of Dental Research* 1995;**74**(Special Issue):138 (Abs No 1013).

Xue 2015 *{published data only}***10.1016/j.bjoms.2015.02.001**

Xue P, Wang J, Wu B, Ma Y, Wu F, Hou R. Efficacy of antibiotic prophylaxis on postoperative inflammatory complications in Chinese patients having impacted mandibular third molars removed: a split-mouth, double-blind, self-controlled, clinical trial. *British Journal of Oral & Maxillofacial Surgery* 2015;**53**:416-20. [DOI: 10.1016/j.bjoms.2015.02.001]

Yoshii 2002 *{published data only}*

Yoshii T, Hamamoto Y, Muraoka S, Furudoi S, Komori T. Differences in postoperative morbidity rates, including infection and dry socket, and differences in the healing process after mandibular third molar surgery in patients receiving 1-day or 3-day prophylaxis with lenampicillin. Journal of Infection & Chemotherapy 2002;**8**(1):87-93.

References to ongoing studies

CTRI/2019/12/022342 *{published data only}*

CTRI/2019/12/022342. Necessity of antibiotic administration following dental extraction- A triple blinded randomized controlled trial [Comparative evaluation of necessity of antibiotic administration following dental extraction among population of age group 30- 60 years - Triple blinded randomized control trial.]. http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=35292&EncHid=&userName=dental%20extraction 12/12/2019.

EudraCT 2017-004986-28 *{published data only}*

*

ZZZ <label> ZZZ*

EudraCT 2017-004986-28. Effect of systemic antibiotic therapy on postoperative complications in patients undergoing wisdom teeth removal surgery. A double-blind, randomised, placebo-controlled Trial [Effect of the usage of antibiotic treatment in patients undergoing wisdom teeth removal surgery]. https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-004986-28/AT First received 2019-02-08.

Additional references

Aida 2009

Aida J, Morita M, Akhter R, Aoyama H, Masui M, Ando Y. Relationships between patient characteristics and reasons for tooth extraction in Japan. *Community Dental Health* 2009;**26**(2):104-9.

Akhter 2008

Akhter R, Hassan NM, Aida J, Zaman KU, Morita M. Risk indicators for tooth loss due to caries and periodontal

disease in recipients of free dental treatment in an adult population in Bangladesh. *Oral Health & Preventive Dentistry* 2008;**6**(3):199-207.

Al-Shammari 2006

Al-Shammari KF, Al-Ansari JM, Al-Melh MA, Al-Khabbaz AK. Reasons for tooth extraction in Kuwait. *Medical Principles & Practice* 2006;**15**(6):417-22.

Anand 2010

Anand PS, Kamath KP, Nair B. Trends in extraction of permanent teeth in private dental practices in Kerala state, India. *Journal of Contemporary Dental Practice* 2010;**11**(3):41-8.

Antibiotic Resistance Threats in the United States

Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S: Centers for Disease Control and Prevention, 2019. [DOI: http://dx.doi.org/10.15620/cdc:82532.]

Arteagoitia 2016

Arteagoitia MI, Barbier L, Santamaría J, Santamaría G, Ramos E. Efficacy of amoxicillin and amoxicillin/clavulanic acid in the prevention of infection and dry socket after third molar extraction. A systematic review and meta-analysis. *Medicina Oral, Patologia Oral y Cirugia Bucal* 2016;**21**(4):e494-504.

Baqain 2007

Baqain ZH, Khraisat A, Sawair F, Ghanam S, Shaini FJ, Rajab LD. Dental extraction for patients presenting at oral surgery student clinic. *Compendium of Continuing Education in Dentistry* 2007;**28**(3):146-50.

Bortoluzzi 2010

Bortoluzzi MC, Manfro R, De Déa BE, Dutra TC. Incidence of dry socket, alveolar infection, and postoperative pain following the extraction of erupted teeth. *Journal of Contemporary Dental Practice* 2010;**11**(1):E033-E040. [PMID: 20098964]

Bouloux 2007

Bouloux GF, Steed MB, Perciaccante VJ. Complications of third molar surgery. *Oral and Maxillofacial Surgery Clinics of North America* 2007;**19**(1):117-28.

Byahatti 2011

Byahatti SM, Ingafou MS. Reasons for extraction in a group of Libyan patients. *International Dental Journal* 2011;**61**(4):199-203.

Chestnutt 2000

Chestnutt IG, Binnie VI, Taylor MM. Reasons for tooth extraction in Scotland. *Journal of Dentistry* 2000;**28**(4):295-7.

Chrysanthakopoulos 2011

Chrysanthakopoulos NA. Reasons for extraction of permanent teeth in Greece: a five-year follow-up study. *International Dental Journal* 2011;**61**(1):19-24.

Costelloe 2010

Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial

resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010;**340**:c2096.

Da'ameh 2006

Da'ameh D. Reasons for permanent tooth extraction in the north of Afghanistan. *Journal of Dentistry* 2006;**34**(1):48-51.

Daly 2012

Daly B, Sharif MO, Newton T, Jones K, Worthington HV. Local interventions for the management of alveolar osteitis (dry socket). *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No: CD006968. [DOI: 10.1002/14651858.CD006968.pub2]

Danielson 2011

Danielson OE, Chinedu AC, Oluyemisi EA, Bashiru BO, Ndubuisi OO. Frequency, causes and pattern of adult tooth extraction in a Nigerian rural health facility. *Odonto-stomatologie Tropicale* 2011;**34**(134):5-10.

Dar-Odeh 2010

Dar-Odeh NS, Abu-Hammad OA, Al-Omiri MK, Khraisat AS, Shehabi AA. Antibiotic prescribing practices by dentists: a review. *Therapeutics and Clinical Risk Management* 2010;**6**:301-6.

Dellinger 1994

Dellinger EP, Gross PA, Barrett TL, Krause PJ, Martone WJ, McGowan JE Jr, et al. Quality standard for antimicrobial prophylaxis in surgical procedures. Infectious Diseases Society of America. *Clinical Infectious Diseases* 1994;**18**:422-7.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

Epstein 2000

Epstein JB, Chong S, Le ND. A survey of antibiotic use in dentistry. *Journal of the American Dental Association* 2000;**131**(11):1600-9.

EU Commission 2011

European Commission Directorate-General for Health & Consumers. Antimicrobial resistance — EU action [Communication (COM(2011 748 final) — Action plan against the rising threats from antimicrobial resistance]. https://eur-lex.europa.eu/legal-content/EN/LSU/?uri=CELEX:52011DC0748 last update 04.10.2019.

EU Commission 2019

Implementation of the EU One Health Action Plan against AMR. European Commission 2019.

Ford 2017

Ford PJ, Saladine C, Zhang K, Hollingworth SA. Prescribing patterns of dental practitioners in Australia from 2001 to 2012. Antimicrobials. *Australian Dental Journal* 2017;**62**(1):52-7.

Ghaeminia 2020

Ghaeminia H, Perry J, Nienhuijs MEL, Toedtling V, Tummers M, Hoppenreijs TJM, et al. Surgical removal versus retention for the

management of asymptomatic disease-free impacted wisdom teeth. *Cochrane Database of Systematic Reviews* 2020, Issue 5. Art. No: CD003879. [DOI: 10.1002/14651858.CD003879.pub5]

Higgins 2017

Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 5.2 (updated June 2017). Cochrane, 2017. Available from training.cochrane.org/handbook/archive/v5.2.

Howe 1985

Howe LH. Minor Oral Surgery. 3rd edition. Bristol: Wright, 1985.

Ioannidis 2009

Ioannidis JP. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. *Archives of Internal Medicine* 2009;**169**(19):1737-9.

Isiordia-Espinoza 2015

Isiordia-Espinoza MA, Aragon-Martinez OH, Martínez-Morales JF, Zapata-Morales JR. Risk of wound infection and safety profile of amoxicillin in healthy patients which required third molar surgery: a systematic review and meta-analysis. *British Journal of Oral & Maxillofacial Surgery* 2015;**53**(9):796-804.

Isiordia-Espinoza 2018

Isiordia-Espinoza MA, Aragon-Martinez OH, Bollogna-Molina RE, Alonso-Castro ÁJ. Infection, alveolar osteitis, and adverse effects using metronidazole in healthy patients undergoing third molar surgery: a meta-analysis. *Journal of Maxillofacial and Oral Surgery* 2018;**17**(2):142-9.

Jaafar 2000

Jaafar N, Nor GM. The prevalence of post-extraction complications in an outpatient dental clinic in Kuala Lumpur Malaysia - a retrospective survey. *Singapore Dental Journal* 2000;**23**(1):24-8.

Jafarian 2013

Jafarian M, Etebarian A. Reasons for extraction of permanent teeth in general dental practices in Tehran, Iran. *Medical Principles and Practice* 2013;**22**(3):239-44.

Jamghili 2016

Jamghili H, Greenwood WJ, Guevara PH, Dunn WJ. Reasons for non-third molar extractions in a military population. *US Army Medical Department Journal* 2016:85-92.

Jovino-Silveira 2005

Jovino-Silveira RC, Caldas Ade F Jr, de Souza EH, Gusmão ES. Primary reason for tooth extraction in a Brazilian adult population. *Oral Health & Preventive Dentistry* 2005;**3**(3):151-7.

Kassebaum 2014

Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJL, Marcenes W. Global burden of severe tooth loss: a systematic review and meta-analysis. *Journal of Dental Research* 2014;**93**(7 Suppl):20S-8S.

Khalil 2015

Khalil D, Hultin M, Andersson FL, Parkbring Olsson N, Lund B. Antibiotic prescription patterns among Swedish dentists working with dental implant surgery: adherence to recommendations. *Clinical Oral Implants Research* 2015;**26**(9):1064-9.

Kim 2017

Kim Min K, Chuang S-K, August M. Antibiotic resistance in severe orofacial infections. *Journal of Oral and Maxillofacial Surgery: Official Journal of the American Association of Oral and Maxillofacial Surgeons* 2017;**75**(5):962-8.

Lee 2015

Lee CY, Chang YY, Shieh TY, Chang CS. Reasons for permanent tooth extractions in Taiwan. *Asia Pacific Journal of Public Health* 2015;**27**(2):Np2350-7.

Lefebvre 2019

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions, Version 6 (updated October 2019). Cochrane, 2019. Available from training.cochrane.org/handbook/archive/v6.

Lesolang 2009

Lesolang RR, Motloba DP, Lalloo R. Patterns and reasons for tooth extraction at the Winterveldt Clinic: 1998-2002. *South African Dental Journal* 2009;**64**(5):214-5, 218.

Lökken 1975

Lökken P, Olsen I, Bruaset I, Norman-Pedersen K. Bilateral surgical removal of impacted lower third molar teeth as a model for drug evaluation: a test with ibuprofen. *European Journal of Clinical Pharmacology* 1975;**8**(3-4):209-16.

Marra 2016

Marra F, George D, Chong M, Sutherland S, Patrick DM. Antibiotic prescribing by dentists has increased: Why? *Journal of the American Dental Association* 2016;**147**(5):320-7.

McCaul 2001

McCaul LK, Jenkins WMM, Kay EJ. The reasons for extraction of permanent teeth in Scotland: a 15-year follow-up study. *British Dental Journal* 2001;**190**(12):658-62.

Menon 2019

Menon RK, Gopinath D, Li KY, Leung YY, Botelho MG. Does the use of amoxicillin/amoxicillin-clavulanic acid in third molar surgery reduce the risk of postoperative infection? A systematic review with meta-analysis. *International Journal of Oral and Maxillofacial Surgery* 2019;**48**(2):263-73.

Passarelli 2020

Passarelli PC, Pagnoni S, Piccirillo GB, Desantis V, Benegiamo M, Liguori A, et al. Reasons for tooth extractions and related risk factors in adult patients: a cohort study. *International Journal of Environmental Research and Public Health* 2020;**17**(7):2575.

Preus 2017

Preus HR, Fredriksen KW, Vogsland AE, Sandvik L, Grytten JI. Antibiotic-prescribing habits among Norwegian dentists: a survey over 25 years (1990-2015). *European Journal of Oral Sciences* 2017;**125**(4):280-7.

Ramos 2016

Ramos E, Santamaría J, Santamaría G, Barbier L, Arteagoitia I. Do systemic antibiotics prevent dry socket and infection after third molar extraction? A systematic review and meta-analysis. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 2016;**122**(4):403-25.

Ren 2007

Ren YF, Malmstrom HS. Effectiveness of antibiotic prophylaxis in third molar surgery: a meta-analysis of randomized controlled clinical trials. *Journal of Oral and Maxillofacial Surgery* 2007;**65**(10):1909-21.

Richards 2005

Richards W, Ameen J, Coll AM, Higgs G. Reasons for tooth extraction in four general dental practices in South Wales. *British Dental Journal* 2005;**198**(5):275-8.

Rücker 2008

Rücker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Statistics in Medicine* 2008;**27**(5):746-63.

Sleeman 1995

Sleeman D, Barry H, Ryan C, Allen F. Day case oral surgery: a review of 25 years experience at the Dublin Dental Hospital. *British Dental Journal* 1995;**179**(6):221-4.

Suda 2019

Suda KJ, Calip GS, Zhou J, Rowan S, Gross AE, Hershow RC, et al. Assessment of the appropriateness of antibiotic prescriptions for infection prophylaxis before dental procedures, 2011 to 2015. *JAMA Network Open* 2019;**2**(5):e193909.

Teoh 2018

Teoh L, Stewart K, Marino RJ, McCullough MJ. Current prescribing trends of antibiotics by dentists in Australia from 2013 to 2016. Part 1. *Australian Dental Journal* 2018;**63**:329-37.

Thomas 1994

Thomas D, Walker R, Smith A, Shepherd J. The provision of oral surgery services in England and Wales 1984-1991. British Dental Journal 1994;**176**(6):215-9.

Thornhill 2019

Thornhill MH, Dayer MJ, Durkin MJ, Lockhart PB, Baddour LM. Risk of adverse reactions to oral antibiotics prescribed by dentists. *Journal of Dental Research* 2019;**98**(10):1081-7.

Thornhill 2019a

Thornhill MH, Dayer MJ, Durkin MJ, Lockhart PB, Baddour LM. Oral antibiotic prescribing by NHS dentists in England 2010-2017. *British Dental Journal* 2019;**227**(12):1044-50.

Trovik 2000

Trovik TA, Klock KS, Haugejorden O. Trends in reasons for tooth extractions in Norway from 1968 to 1998. *Acta Odontolologica Scandinavica* 2000;**58**(2):89-96.

Worthington 1999

Worthington H, Clarkson J, Davies R. Extraction of teeth over 5 years in regularly attending adults. *Community Dentistry and Oral Epidemiology* 1999;**27**(3):187-94.

References to other published versions of this review

Lodi 2012

Lodi G, Figini L, Sardella A, Carrassi A, Del Fabbro M, Furness S. Antibiotics to prevent complications following tooth extractions. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No: CD003811. [DOI: 10.1002/14651858.CD003811.pub2]

* Indicates the major publication for the study

C H A R A C T E R I S T I C S O F S T U D I E S

Characteristics of included studies *[ordered by study ID]*

Arteagoitia 2005

Study characteristics	
Methods	Study design: RCT
	Conducted in: Spain
	Number of centres: 1
	Recruitment period: between March 2001 and February 2003
	Funding source: financed by the Health Research Fund FIS/GRAN dossier number 00/0585. Trial participant insurance was taken out by the Basque Health Department, Basque Health Service/Osakidetza, Osakidetza, pursuant to the conditions laid down in RD 561/1993. The antibiotic and placebo were sup-

Arteagoitia 2005 *(Continued)*

plied free of charge by Géminis (Novartis generics). Chlorhexidine was supplied free of charge by LAC-ER.

Participants	Inclusion criteria: people needing a third molar extraction under local anaesthesia
	Exclusion criteria: people with any bacterial endocarditis risk factors, pregnant and breastfeeding women, people with acute infections 10 days prior to the intervention, those who had to take antibiotics, and those with a history of allergy or intolerance to the drugs used
	Age: mean 24 years, range 18 to 60 years
	Group A: randomised 233, analysed 233 (ITT analysis)
	Group B: randomised 261, analysed 261 (ITT analysis)
Interventions	**Comparison: postoperative amoxicillin/clavulanate versus placebo**
	Group A: amoxicillin/clavulanic acid 500/125 mg oral 3 times a day for 4 days after the procedure
	Group B: placebo oral 3 times a day for 4 days after the procedure
	All participants had irrigation of the alveolus with 0.12% chlorhexidine digluconate, and chlorhexidine mouthwashes were used for 3 days.
Outcomes	Fever (oral temperature > 37.8 after 24 hours for no other justifiable cause); intraoral abscess diagnosed via fluctuation pus drainage; dry socket defined as absence of clot with necrotic remains present in the alveolus accompanied by severe mandibular pain; severe pain persisting or increasing 48 hours after surgery accompanied by intraoral inflammation (moderate or severe) and/or intraoral erythema (moderate or severe); severe pain after day 7 accompanied by intraoral inflammation (moderate or severe) and/or intraoral erythema (moderate or severe). Lack of inflammatory complications. Diagnosis of postoperative infection and inflammatory complication was performed by the main researcher.
	Adverse events (number of episodes).
Notes	All extractions were performed by maxillofacial surgeons, under locoregional anaesthetic of the inferior alveolar and buccal nerves with Ultracain.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation codes generated by the C4-SDP software MAS Module"
Allocation concealment (selection bias)	Low risk	Quote: "Each of enrolled patients was assigned the corresponding blinded random successive treatment number"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants lost to follow-up from each group but intention-to-treat analysis was performed.

Arteagoitia 2005 *(Continued)*

Selective reporting (reporting bias)	High risk	Planned outcomes of pain, inflammation and erythema measured qualitatively and reported, but VAS pain scores measured and not reported.
Other bias	Low risk	No other sources of bias identified.

Arteagoitia 2015

Study characteristics	
Methods	Study design: RCT
	Conducted in: Spain
	Number of centres: 1
	Recruitment period: unspecified
	Funding source: the study was funded by a grant (EC-08/00068) from the Carlos III Health Institute of the Spanish Ministry of Health, Social Services and Equality
Participants	Inclusion criteria: participants "over 18 years old undergoing completely bone-impacted lower third molar (4.8 or 3.8) removal for any indication were candidates for the study"
	Exclusion criteria: pregnancy or breastfeeding, having unstable systemic diseases, risk factors for endocarditis, an infection or antibiotics in the preceding 10 days, or an allergy or known intolerance to any study medication
	Age: mean 28.47 years
	Group A: randomised 61, analysed 60
	Group B: randomised 61, analysed 58
Interventions	**Comparison: pre- and postoperative amoxicillin/clavulanic acid versus placebo**
	Group A: 2 g amoxicillin/125 mg clavulanic acid 2 hours before the surgery and postoperatively twice a day for 4 days
	Group B: placebo 2 hours before the surgery and postoperatively twice a day for 4 days
	All participants were given a box of 40 sachets of ibuprofen 600 mg and a 200 mL bottle of 0.12% chlorhexidine mouthwash.
Outcomes	Infection (primary outcome) was defined on the basis of: C-reactive protein 2.2 mg/dL, body temperature > 37.8 °C for over 24 hours with no other identifiable cause; intraoral abscess diagnosed by fluctuation or pus discharge; severe pain persisting or increasing 48 hours after surgery accompanied by intraoral inflammation (moderate or severe); intraoral erythema and/or limited mouth opening; severe pain after day 7 accompanied by intraoral inflammation (moderate or severe) and/or intraoral erythema (moderate or severe) with no other identifiable cause which improves with antibiotic treatment.
	Intraoral and extraoral erythema (on a 4-grade scale), intraoral oedema (on a 4-grade scale), alveolitis (dry socket: presence/absence), trismus (mouth opening mm), pain on intra- and extra-oral palpation (on a 4-grade scale), CRP blood levels (mean). All values were recorded 7 days after surgery.
	Adverse events up to day 7 after surgery (number of events).
Notes	The 2 groups were significantly different at baseline in terms of age (mean: 25.57 years in group A and 31.48 in group B) and mouth opening (mean opening 52.01 mm in group A and 49.09 mm in group B).

Arteagoitia 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation codes generated by the C4-SDP software MAS Module"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants in both groups received tablets in an opaque bottle, plus the Hospital Pharmacy Unit was in charge of the management of the medication.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants in both groups received tablets in an opaque bottle, plus the Hospital Pharmacy Unit was in charge of the management of the medication. In addition "a single blinded observer assessed the post-operative variables for each patient".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition bias unlikely as only 4 of 122 participants were not included in trial analysis (1 in test group and 3 in placebo group).
Selective reporting (reporting bias)	Low risk	All planned outcomes described in the published protocol (EudraCT Number: 2008-005663-34) were reported.
Other bias	Low risk	No other sources of bias identified.

Barclay 1987

Study characteristics

Methods	Study design: RCT
	Conducted in: New Zealand
	Number of centres: 1
	Recruitment period: unspecified
	Funding source: metronidazole and placebo tablets were supplied by May and Baker New Zealand Ltd
Participants	Inclusion criteria: people "with a history of non-acute pericoronitis, and therefore likely to experience a high prevalence of dry socket". Participants had to meet 2 or more of the following criteria: a history of 2 or more episodes of previously diagnosed pericoronitis; the expression of pus from beneath a pericoronal flap in the absence of significant symptoms; radiographic enlargement of the follicular space distal to the third molar in the absence of significant symptoms; crater-like radiographic defect as described by Howe (Howe 1985).
	Exclusion criteria: pregnancy
	Age: mean 23 years, range 16 to 48 years
	Group A: randomised 50, analysed 45
	Group B: randomised 50, analysed 50

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Barclay 1987 *(Continued)*

Interventions	**Comparison: pre- and postoperative metronidazole versus placebo**
	Group A: metronidazole 400 mg 1 hour before the intervention and then 3 times a day for 8 times
	Group B: placebo 1 hour before the intervention and then 3 times a day for 8 times
	All participants were given the same postoperative instructions and 6 analgesic tablets (codeine phosphate and paracetamol).
Outcomes	Dry socket: continuous dull pain from an empty, or partially empty, socket, or from the region of the socket
	Adverse events (number of events)
Notes	Pain was compared between participants with and without dry socket only, thus quantitative analysis was not possible.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Assigned to one of two groups by a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind Quote: "none of the patients, nor the several operators, were aware of the active or placebo nature of the individual medication"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind Quote: "none of the patients, nor the several operators, were aware of the active or placebo nature of the individual medication"
Incomplete outcome data (attrition bias) All outcomes	High risk	10% of antibiotic group not included in the analysis.
Selective reporting (reporting bias)	Low risk	Planned outcomes of dry socket, pain (VAS), adverse events, and compliance reported.
Other bias	Low risk	No other sources of bias identified.

Bergdahl 2004

Study characteristics

Methods	Study design: RCT
	Conducted in: Sweden
	Number of centres: 1
	Recruitment period: unspecified

Bergdahl 2004 *(Continued)*

	Funding source: unspecified
Participants	Inclusion criteria: healthy people, not taking any other drugs apart from oral contraceptives, who needed removal of unilateral or bilateral mandibular third molar teeth. Only partially impacted teeth, which had partly broken through the mucosa, with a communication to the oral cavity, requiring surgical flap, were included in the study.
	Exclusion criteria: participants with teeth completely covered with mucosa
	Age: mean 23 years, range 17 to 30 years
	Group A: randomised 60, analysed 59
	Group B: randomised 60, analysed 60
Interventions	**Comparison: preoperative metronidazole versus placebo**
	Group A: metronidazole 1600 mg as a single dose 45 min before the intervention
	Group B: placebo as a single dose 45 min before the intervention
	All participants were given the same postoperative instructions and 20 analgesic tablets (paracetamol 500 mg with codeine 30 mg).
Outcomes	Dry socket assessed 4 days postoperatively
Notes	Participants with acute pericoronitis were operated on after objective and subjective symptoms of pericoronitis had ceased.
	Sample size calculation reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "a randomised trial". Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only "one patient had to be withdrawn because he had taken an oral antibiotic for other reasons two days after operation".
Selective reporting (reporting bias)	High risk	The outcomes pain, bad odour or taste as assessed by participants were not reported.
Other bias	Unclear risk	Short duration of follow-up (4 days). Unclear whether participants with acute pericoronitis prior to trial were treated with antibiotics

Bezerra 2011

Study characteristics

Methods	Study design: RCT cross-over
	Conducted in: Brazil
	Number of centres: 1
	Recruitment period: January to November 2008
	Funding source: unspecified
Participants	Inclusion criteria: healthy patients with no periodontal disease requiring removal of 4 third molars, with similar degrees of impaction between sides of mouth
	Exclusion criteria: tobacco use, orthodontic bands on second molars, pregnancy or breastfeeding, chronic systemic disorders, allergies to antibiotics, history of adverse events from antibiotics, and use of antibiotics in 3 months prior to entering trial
	Age: mean 21 years, range 18 to 31 years
	Number randomised: 36
	Number evaluated: 34
Interventions	**Comparison: preoperative amoxicillin versus placebo**
	Group A: amoxicillin 2 x 500 mg administered orally 1 hour preoperatively
	Group B: placebo (2 tablets) identical in appearance administered 1 hour preoperatively
	Standard painkiller recommendation included nimesulide (nonsteroidal anti-inflammatory drug) 100 mg every 12 hours for 4 days and dipyrone (nonsteroidal anti-inflammatory drug) 500 mg 6 hourly for 2 days.
Outcomes	Soft tissue oedema/ulcer, pain (1-to-10 VAS at 7th day), oedema, limitation of mouth opening, infection (purulent secretion), alveolitis (pain + partially/totally disintegrated clot), fever at 3, 7, and 14 days postoperatively (not reported in the Results section, see 'Risk of bias' table)
Notes	Email from author 13 February 2012 stating that duration of washout period was at least 45 days. Additional outcome data provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drugs/placebo placed into transparent, sterile boxes with code number. Participant chose 1 box for first procedure, and a coin toss decided which side of mouth was done first.
Allocation concealment (selection bias)	Low risk	Unclear who performed the coin toss and how the result was communicated to the surgeon. However, bias is unlikely to result from this design.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind – neither participant nor surgeon knew which treatment was given

Bezerra 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind – neither participant nor surgeon knew which treatment was given
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/36 participants were not included in analysis. Due to low number and cross-over design, attrition bias is unlikely.
Selective reporting (reporting bias)	High risk	Fever was mentioned in the Methods section but not reported in the Results.
Other bias	Low risk	No other sources of bias identified.

Bortoluzzi 2013

Study characteristics	
Methods	Study design: RCT
	Conducted in: Brazil
	Number of centres: 1
	Recruitment period: unspecified
	Funding source: this research was partially supported by Fundacao de Amparo a Paesquisa e Inovacao do Estado de Santa Catarina (FAPESC) and Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq)
Participants	Inclusion criteria: participants underwent surgical removal of a single mandibular third molar, must be considered healthy or meet the American Society of Anesthesiologists classification status I (ASA I - normal healthy patients); all participants were submitted to blood tests (complete blood count and blood glucose) to confirm health condition.
	Exclusion criteria: participants with anaemia (haemoglobin of < 13 g/dL in males - a haematocrit (Hct) of about 39; and < 12 g/dL in females - Hct about 36) or with total leucocytes count < 4000 cells/mL or neutrophils < 2000 cells/mL (as well as leukocytosis), patients with glucose parameters beyond normal limits (65 to 110 g/dL); history of allergy, recent uses of antibiotics, active pericoronitis (local infection with presence of symptom or pus) and fractured root left in the socket.
	Age: mean G1 23.2, G2 22.8, G3 21.5, G4 22.5
	Group 1: randomised 12, analysed 12
	Group 2: randomised 12, analysed 12
	Group 3: randomised 14, analysed 14
	Group 4: randomised 12 analysed 12
Interventions	**Comparison: preoperative amoxicillin with or without dexamethasone versus placebo**
	Group 1: 2 g of amoxicillin and 8 mg of dexamethasone between 1 and 1½ hours before surgery
	Group 2: 2 g of amoxicillin and 8 mg of placebo between 1 and 1½ hours before surgery
	Group 3: 2 g of placebo and 8 mg of dexamethasone between 1 and 1½ hours before surgery
	Group 4: 2 g of placebo and 8 mg of placebo between 1 and 1½ hours before surgery

Bortoluzzi 2013 *(Continued)*

Outcomes	Alveolar osteitis; alveolar infection; pain (self-rated through a VAS (0 to 100), 10 times in the course of 5 days, starting at 5 and 6 hours after surgery, at waking time, and at the end of the day (standardised between 6.00 and 8.00 PM) for days 1 to 3 and end of the day for days 4 and 5); oedema (based on participant experience (self-rated) through a VAS (0 to 100), evaluated 5 times always at the end of the day and starting at the end of the first postoperative day); trismus (evaluated according to its presence or absence based on clinical observation and participant report of having any significant limitation of mouth opening, i.e. half of normal mouth opening)
Notes	Only data from Groups 2 and 4 were evaluated in the current review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details were provided on the method employed (raffle).
Allocation concealment (selection bias)	Unclear risk	No details were provided on the method employed (raffle).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both drugs AMO and DEX were bought form commercially available and re-packed in a compounding pharmacy to standardize the color of capsules. Both drugs and placebo were then packaged together according to the group to ensure the blinding and the random process"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "both drugs AMO and DEX were bought form commercially available and re-packed in a compounding pharmacy to standardize the color of capsules. Both drugs and placebo were then packaged together according to the group to ensure the blinding and the random process"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the primary outcome assessment.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Low risk	No other sources of bias identified.

Bystedt 1980

Study characteristics

Methods	Study design: RCT Conducted in: Sweden Number of centres: 1 Recruitment period: unspecified Funding source: unspecified
Participants	Inclusion criteria: healthy people requiring surgical removal of impacted third molar of mandible Exclusion criteria: history of significant gastric, hepatic, or renal disease, those taking any other medication except analgesia during study period

Bystedt 1980 *(Continued)*

	Age: mean 29 years, range 17 to 79 years
	Number randomised: 140 in 3 separate subtrials
	Number evaluated: unclear, reported as percentage of combined groups
Interventions	**Comparison A: 1 hour preoperative + 7 days postoperative azidocillin versus placebo**
	Comparison B: 90 min preoperative + 7 days postoperative erythromycin or clindamycin versus placebo
	Comparison C: 180 min preoperative + 7 days postoperative doxycycline versus placebo
	Study A (n = 40): either azidocillin 750 mg 1 hour preoperative + 750 mg twice a day for 7 days postoperative or matching placebo
	Study B (n = 60): either erythromycin stearate 500 mg or clindamycin 300 mg or placebo 90 min preoperative followed by 250 mg erythromycin or 150 mg clindamycin or placebo 4 times daily for 7 days
	Study C (n = 40): either 200 mg doxycycline or placebo 180 min preoperative plus either 100 mg doxycycline or placebo once daily for 7 days
	All participants had 0.5 to 1 g acetylsalicylic acid as needed for pain.
Outcomes	Capillary serum antibiotic levels, dental alveolar blood antibiotic levels, bone antibiotic levels, evaluated on day 2. Duration of operation, pain, trismus, swelling, wound healing, side effects evaluated on days 2, 5, and 7 postoperatively.
Notes	This study was only included in qualitative analysis because it was not possible to extract data of the 3 different trials.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "assigned at random". Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers of participants allocated to antibiotic or placebo not explicitly stated for each of the subtrials, and numbers evaluated not stated for each subtrial for each outcome.
Selective reporting (reporting bias)	High risk	All planned outcomes reported, but not for each randomised treatment group, and no estimates of variance given for pain.
Other bias	Unclear risk	No description of characteristics of participants by randomised group at baseline

Bystedt 1981

Study characteristics

Methods	Study design: 3-arm RCT
	Conducted in: Sweden
	Number of centres: 1
	Recruitment period: unspecified
	Funding source: unspecified
Participants	Inclusion criteria: healthy participants referred for surgical removal of an impacted third molar of the mandible
	Exclusion criteria: unspecified
	Age: range 17 to 30 years
	Group A: randomised 20, analysed 20
	Group B: randomised 20, analysed 20
	Group C: randomised 20, analysed 20
Interventions	**Comparison: pre- and postoperative penicillin versus pre- and postoperative azidocillin versus placebo**
	Group A: phenoxymethylpenicillin 800 mg 1 hour before operation and then twice a day (at 9.00 AM and 9.00 PM) for 7 days
	Group B: azidocillin 750 mg 1 hour before operation and then twice a day (at 9.00 AM and 9.00 PM) for 7 days
	Group C: placebo 1 hour before operation and then twice a day (at 9.00 AM and 9.00 PM) for 7 days
	Aspirin 0.5 to 1.0 g was provided to all participants as a rescue analgesic to be taken when needed. No other medications except analgesics were allowed during the investigation period.
Outcomes	Pain was measured on the day of operation and on days 2, 5, and 7 on a 3-grade scale (I none or insignificant, II pain requiring no analgesic, III severe pain requiring analgesic)
	Trismus was measured on the day of operation and on days 2, 5, and 7 measuring the ability to open the mouth, using a vernier gauge.
	Extraoral swelling was measured according to the method described by Lökken 1975.
	Dry socket diagnosis was made clinically on the basis of severe mandibular pain accompanied by necrotic debris or a denuded alveolus.
	Wound healing (evidence of loose of periosteal flap and alveolitis)
	Adverse events: participants were questioned at each examination regarding adverse events such as fever, indisposition, or diarrhoea
Notes	The only useable data that could be extracted were on dry socket, participants with no complications, and adverse events. Groups A and B have been considered together in the analysis.
	All operations were carried out under local anaesthesia by the same surgeons.

Risk of bias

Bystedt 1981 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were assigned at random". Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data. All randomised participants included in results analysis.
Selective reporting (reporting bias)	High risk	Data for swelling and trismus not reported, only mentioned that there was no difference.
Other bias	Low risk	No other sources of bias identified.

Gbotolorun 2016

Study characteristics	
Methods	Study design: 2-arm RCT
	Conducted in: Nigeria
	Number of centres: 1
	Recruitment period: unspecified
	Funding source: none
Participants	Inclusion criteria: males and females aged between 20 and 50 years who required a routine intra-alveolar extraction
	Exclusion criteria: people with chronic oral infections, immune-compromised, pregnant and lactating women, receiving chemotherapy or radiation therapy, already on antibiotics before seeking care at the hospital, needing total extraction or with severe periodontitis or any other oral pathology
	Age: 30.6 +/- 9.3 years
	Group A: randomised 86, analysed 75
	Group B: randomised 85, analysed 75
Interventions	**Comparison: postoperative amoxicillin plus metronidazole versus postoperative placebo**
	Group A: amoxicillin 500 mg plus metronidazole 400 mg 3 times a day for 5 days postoperatively
	Group B: placebo plus placebo 3 times a day for 5 days postoperatively

Gbotolorun 2016 *(Continued)*

All participants received paracetamol 1000 mg every 8 h for 3 days, and vitamin C 100 mg every 8 h for 2 weeks.

Outcomes	Normal healing alveolus: a healing alveolus with decreasing pain or without pain, with evidence of gradual or complete socket closure
	Dry socket: persistent or increased postoperative pain in and around the extraction site, accompanied by a partially or totally disintegrated blood clot or an empty socket, with or without halitosis; the diagnosis is confirmed when extremely sensitive bare bone is encountered when passing a small curette into the extraction wound
	Acutely inflamed socket: painful socket with inflamed tissue, but without pus or systemic fever
	Acutely infected socket: painful socket with suppuration, erythema, and oedema, with or without systemic fever
	Pain was assessed using a 4-point verbal rating scale (VRS) and categorised as follows: 1 = no pain (no pain experienced); 2 = mild pain (pain almost unnoticeable); 3 = moderate pain (noticeable pain, but does not disturb daily activities); 4 = severe pain (very noticeable pain that disturbs daily activities).
	All outcomes were assessed on days 1, 3, and 7 postoperatively.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants, consecutively recruited, were allocated randomly to the antibiotics or placebo group by picking tallies pre-marked A or B from a box.
Allocation concealment (selection bias)	Low risk	Participants, consecutively recruited, were allocated randomly to the antibiotics or placebo group by picking tallies pre-marked A or B from a box.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the participant nor the postoperative assessor knew the treatment assigned to the group they had picked.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither the participant nor the postoperative assessor knew the treatment assigned to the group they had picked.
Incomplete outcome data (attrition bias) All outcomes	Low risk	21 participants lost during the study, 11 from Group A, 10 from Group B. Due to the relatively low and balanced number of participants lost to follow-up, it is probable that this attrition did not represent a bias.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Low risk	No other sources of bias identified.

Halpern 2007

Study characteristics

Methods	Study design: RCT
	Conducted in: USA

Halpern 2007 *(Continued)*

Number of centres: 1

Recruitment period: between 1 June 2002 and 1 July 2005

Funding source: supported in part by the Oral and Maxillofacial Surgery Foundation Research Grant and Massachusetts General Hospital (MGH) Center for Applied Clinical Investigation

Participants	Inclusion criteria: people needing a third molar extraction under intravenous sedation or general anaesthesia in the office-based ambulatory setting
	Exclusion criteria: people with pre-existing conditions that could affect wound healing or predispose them to inflammatory complications, including previous radiation therapy to the maxillofacial region, HIV infection, organ or marrow transplant candidates or recipients, diabetes, or organ failure (kidney, heart, liver); patients requiring antibiotic prophylaxis for endocarditis, or currently on oral steroid therapy, or allergic to the antibiotics proposed for use in this study, deferred intravenous sedation or general anaesthesia; had local pathology, e.g. cysts or tumour, associated with M3s that was not incidental to the removal of the M3; acute inflammation in the area of the planned extraction characterised by frank purulence, erythema, induration, or trismus; supernumerary teeth to be removed; or deferred study participation
	Age: mean 25 years
	Group A: randomised 60, analysed 59
	Group B: randomised 62, analysed 59
Interventions	**Comparison: preoperative intravenous penicillin (or clindamycin) versus placebo**
	Group A: solution of penicillin (15,000 units per kilogram) or, for penicillin-allergic people, clindamycin (600 mg) administered intravenously within 1 hour before the intervention
	Group B: placebo solution (10 cm^3 saline 0.9%) administered intravenously within 1 hour before the intervention
	Postoperative analgesia consisted of the use of 1 or 2 paracetamol (500 mg) and hydrocodone (5 mg) tablets administered orally every 3 to 4 hours.
Outcomes	Dry socket (a new-onset or increasing pain more than 36 hours after the operation, with a loss of the blood clot in the extraction site as evidenced by exposed bone, gentle probing or irrigation of the wound duplicating the pain, and significant pain relief after application of an anodyne dressing; all elements needed to be present to make the diagnosis)
	Surgical site infection (visual evidence of frank purulence in 1 or more of the extraction sites and a Gram's stain demonstrating white blood cells present): assessed on day 7 postoperatively (range 5 to 14)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". Method of sequence generation not described.
Allocation concealment (selection bias)	Low risk	Quote: "consecutively numbered, double-sealed envelopes were prepared containing the treatment assignment"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double blind. The surgeon and study participant were blinded to the true nature of the contents of the syringe"

Halpern 2007 *(Continued)*

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind. The surgeon and study participant were blinded to the true nature of the contents of the syringe"
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/60 and 3/62 participants lost to follow-up in the antibiotic and placebo groups. Due to the relatively low and balanced number of participants lost to follow-up, it is probable that this attrition did not represent a bias.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Low risk	No other sources of bias identified.

Happonen 1990

Study characteristics

Methods	Study design: 3-arm RCT
	Conducted in: Finland
	Number of centres: 1
	Recruitment period: unspecified
	Funding source: unspecified
Participants	Inclusion criteria: healthy people seeking treatment for impacted teeth, not on any drugs with the exception of oral contraceptives
	Exclusion criteria: hypersensitivity to penicillin or codeine
	Age: mean 24 years
	Group A: randomised unclear, analysed 44
	Group B: randomised unclear, analysed 47
	Group C: randomised unclear, analysed 45
	8 of the enrolled participants (total 144) were not included in the analysis, but it is unclear to which group they had been allocated.
Interventions	**Comparison: pre- and postoperative penicillin versus pre- and postoperative tinidazole versus placebo**
	Group A: 1 tablet of phenoxymethylpenicillin 660 mg 1 hour before operation and then 3 times a day for 14 times
	Group B: 1 tablet of tinidazole 500 mg 1 hour before operation and then 3 times a day for 14 times
	Group C: 1 tablet of placebo 1 hour before operation and then 3 times a day for 14 times
	A 1-minute mouth rinse of 0.2% chlorhexidine was given before surgery.
	3 tablets of a preparation containing aminophenazone (300 mg), phenobarbital (50 mg), codeine (30 mg), and caffeine (100 mg) was provided to all participants as a rescue analgesic to be taken when needed.

Happonen 1990 *(Continued)*

Outcomes	Time of onset and resolution of postoperative swelling, as well as time of maximum swelling, as recorded by participants
	Postoperative pain every hour during the day of the surgery, and at intervals of 4 and 6 hours on the first and second postoperative day, respectively. Number of analgesics was also reported.
	Maximal opening of the mouth was measured before and after surgery (sixth day).
	Participants were visited on the sixth postoperative day and signs of infection, fever, swelling, and tender lymph nodes were recorded by the clinicians.
Notes	Group A and B were considered together in the current review.
	All operations were carried out under local anaesthesia, by 1 surgeon, using a standardised procedure, 1 tooth operated at a time.
	An author is the project manager of the company that provided the tablets.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned". Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	High risk	8 out of 144 participants were lost at follow-up (5%), and it is unclear which groups these were from. No specific ITT approach is adopted.
Selective reporting (reporting bias)	High risk	Planned outcomes of duration of swelling, infection, fever reported. Pain (VAS) reported only in graph for first 13 hours, no data at day 7, yet this was the main reason given for time off work.
Other bias	Low risk	No other sources of bias identified.

Kaczmarzyk 2007

Study characteristics

Methods	Study design: 3-arm RCT
	Conducted in: Poland
	Number of centres: 1
	Recruitment period: between January 2005 and April 2006

Kaczmarzyk 2007 *(Continued)*

	Funding source: unspecified
Participants	Inclusion criteria: participants needing surgical extraction of a retained lower third molar, which was not the cause of inflammation (mainly due to orthodontic recommendations) that required bone removal
	Exclusion criteria: age under 18 or over 60, pregnancy, allergy to clindamycin, lactose intolerance (lactose was the main component of the placebo), episodes of diarrhoea after antibiotic therapy in the interview, any digestive diseases, inflammation in the area of the tooth to be extracted, and any antibiotic or analgesic intake within the previous 7 days
	Age: mean 24 years
	Group A: randomised unclear, analysed 31
	Group B: randomised unclear, analysed 28
	Group C: randomised unclear, analysed 27
	Of the 100 participants enrolled, 9 did not check in for the follow-up examination; 3 were disqualified due to complications; and 2 resigned during the trial without providing any reason.
Interventions	**Comparison: preoperative versus pre- and postoperative clindamycin versus placebo**
	Group A: single-dose group: participants receiving 600 mg clindamycin hydrochloride orally 60 min preoperatively, followed by a 300 mg placebo every 8 hours for 5 days
	Group B: 5-day group: participants receiving 600 mg clindamycin hydrochloride orally 60 min preoperatively, followed by a dose of 300 mg clindamycin hydrochloride every 8 hours for 5 days
	Group C: placebo group: participants receiving 600 mg placebo orally 60 min prior to surgery, followed by a dose of 300 mg placebo every 8 hours for 5 days
	Only groups B and C were considered for the current review.
Outcomes	The following outcomes were evaluated on the first, second, and seventh postoperative day: trismus (on a 4-grade scale), facial swelling (on a 4-grade scale), submandibular lymphadenopathy (on a 4-grade scale), body temperature, pain (on a 100-millimetre VAS), alveolar osteitis (clinical diagnosis of this complication was made in the presence of a necrotic grey clot in a bare bony socket, foetor ex ore, accompanied by pain in this area), adverse events (number of events).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "group assignment for one subject, determined in advance by a random number table"
Allocation concealment (selection bias)	Low risk	Quote: "one hundred opaque and sequentially numbered envelopes were used for the concealment of allocation to trial groups"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the subjects, the surgeon performing the qualification, operative procedure and follow-up examination, and the statistician were not aware of who received which study intervention"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the subjects, the surgeon performing the qualification, operative procedure and follow-up examination, and the statistician were not aware of who received which study intervention"

Kaczmarzyk 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	14 out of 100 participants were lost at follow-up (14%). No specific ITT approach is adopted, and it is unclear which groups these participants were from.
Selective reporting (reporting bias)	Low risk	Planned outcomes of postoperative inflammation (swelling, lymphadenopathy, trismus), pain, body temperature, and alveolar osteitis reported.
Other bias	Low risk	No other sources of bias identified.

Kaziro 1984

Study characteristics

Methods	Study design: 3-arm RCT
	Conducted in: UK
	Number of centres: 1
	Recruitment period: unspecified
	Funding source: a company supplied metronidazole and placebo tablets, arnica tablets were supplied by the Royal London Homoeopathic Hospital
Participants	Inclusion criteria: participants with impacted mandibular wisdom teeth
	Exclusion criteria: unspecified
	Age: unspecified
	Group A: randomised 41, analysed unclear
	Group B: randomised 39, analysed unclear
	Group C: randomised 38, analysed unclear
Interventions	**Comparison: postoperative metronidazole versus arnica versus placebo**
	Group A: metronidazole 400 mg 1 tablet twice daily for an unspecified length of time
	Group B: arnica 200 mg tablets 1 tablet twice daily for an unspecified length of time
	Group C: placebo 1 tablet twice daily for an unspecified length of time
	All participants had 2 Codis (aspirin plus codeine) tablets 3 times daily for 3 days for pain.
	Only groups A and C were considered for the current review.
Outcomes	Pain, trismus, oedema, wound healing on fourth and eighth postoperative day, wound breakdown
Notes	Data presented in graphs only. This study was thus only included in qualitative analysis because it was not possible to extract data. Extractions were done by 1 of 6 surgeons blinded to allocated treatment. All interventions were provided under general anaesthesia.

Risk of bias

Bias	Authors' judgement	Support for judgement

Kaziro 1984 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quotes: "randomised allocation" "randomly divided". Method of sequence generation not described.
Allocation concealment (selection bias)	Low risk	Code was kept by pharmacist at Royal London Homeopathic Hospital.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants that completed the trial is not specified.
Selective reporting (reporting bias)	High risk	All planned outcomes reported, but data only presented in graphs.
Other bias	Unclear risk	No description of characteristics of participants by randomised groups at baseline

Lacasa 2007

Study characteristics

Methods	Study design: 3-arm RCT
	Conducted in: Spain
	Number of centres: 1
	Recruitment period: between January and December 2002
	Funding source: the trial was supported by a grant from GlaxoSmithKline S.A., Tres Cantos, Madrid, Spain
Participants	Inclusion criteria: adults (> 18 years of age) with planned third mandibular molar surgery
	Exclusion criteria: a recent local infection prior to surgery (< 15 days), known or suspected allergy to beta-lactams, known or suspected allergy to metamizole, history of renal failure, blood dyscrasia or chronic liver disease of any type, antecedents of recent and/or symptomatic peptic ulcer, or were on antiaggregant or corticosteroids prior to entry (< 15 days). Females of childbearing potential had to have a negative urine pregnancy test prior to enrolment.
	Age: mean 29 years
	Group A: randomised 75, analysed (day 7) 62
	Group B: randomised 75, analysed (day 7) 68
	Group C: randomised 75, analysed (day 7) 69
Interventions	**Comparison: preoperative versus postoperative amoxicillin/clavulanate versus placebo**
	Group A: 2 placebo tablets in a single dose before surgery, plus 1 placebo tablet twice a day for 5 days

Lacasa 2007 *(Continued)*

Group B: 2 amoxicillin/clavulanate 1000/62.5 mg tablets in a single dose before surgery, followed by 1 placebo tablet twice a day for 5 days

Group C: 2 placebo tablets in a single dose before surgery, followed by 1 amoxicillin/clavulanate 1000/62.5 mg tablet twice a day for 5 days

All participants were matched to receive the same analgesic drug throughout the study period with identical dosage. Metamizole (Nolotil capsules) was used, 1 capsule every 8 hours, for a minimum of 48 hours, because it is much less anti-inflammatory than other analgesics. Participants were allowed to continue receiving analgesia afterwards (according to the investigator's judgement), depending on the presence of pain.

Outcomes	The main study variables were evaluated on days 1, 3, and 7.
	Infection was defined by any of the following: (1) presence of purulent discharge in the extraction socket and/or excessive swelling with fluctuation, with or without pain; (2) presence of a local abscess; (3) onset of facial or cervical cellulitis plus other signs suggesting infection such as pain, increased heat, erythema and/or fever; (4) presence of osteitis of dental alveolus defined as absence of the haematic clot of the orifice and presence of a putrid smell and intense neuralgic-type pain.
	Other inflammatory outcomes were recorded individually, and in a composite way using an inflammation score tabular display with a maximum permitted score of 10. They included swelling, trismus, pain, dysphagia, fever.
	Adverse events (number of events)
Notes	2 of the authors are employees of the funding company.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	High risk	It is unclear whether the authors used any ITT analysis. 3/225, 9/225, and 26/225 participants were lost to follow-up at days 1, 3, and 7 respectively, and they are not balanced between the groups.
Selective reporting (reporting bias)	High risk	The planned outcomes according to the methods were infection, inflammation, swelling, trismus, pain, dysphagia, fever, and adverse events. Data were reported for infection and means without variance estimates for pain, but no other outcome data reported.
Other bias	Unclear risk	Statistically significant difference in duration of operation between the placebo and pre-emptive groups

Leon Arcila 2001

Study characteristics

Methods	Study design: RCT
	Conducted in: Colombia
	Number of centres: 1
	Recruitment period: 1 September 1998 to 1 September 2000
	Funding source: unspecified
Participants	Inclusion criteria: patients aged 14 to 53 years, ASA1, with good oral hygiene, bacterial plaque index </= 30%, no oral cavity infections or inflammation or pericoronitis, who required extraction of third molars
	Exclusion criteria: allergy to penicillin
	Age: unspecified
	Group A: randomised 49, analysed 49
	Group B: randomised 53, analysed 53
Interventions	**Comparison: pre- and postoperative amoxicillin versus placebo**
	Group A: amoxicillin 1 g orally 1 hour preoperatively and 6 hours postoperatively
	Group B: placebo 1 hour preoperatively and 6 hours postoperatively
Outcomes	Infectious complications assessed on days 5 and 10 postoperatively.
Notes	All participants had a single extraction - 38 upper teeth and 64 lower teeth.
	Additional information supplied by author in response to email request.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomised using a computer" (email from author)
Allocation concealment (selection bias)	Low risk	Quote: "one of the researchers allocated the treatment. Surgeon, patient and statistician did not know such information" (email from author)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "no drop outs or losses to follow up. Everybody was included" (email from author)

Leon Arcila 2001 *(Continued)*

Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Low risk	No other sources of bias identified.

López-Cedrún 2011

Study characteristics		

Methods	Study design: RCT
	Conducted in: Spain
	Number of centres: 1
	Recruitment period: unspecified
	Funding source: unspecified

Participants	Inclusion criteria: at least 1 mandibular impacted or partially erupted third molar requiring extraction
	Exclusion criteria: people aged > 60 or < 18 years, infectious or systemic diseases, immunosuppressive treatment, smoking, peptic ulcer, pregnancy, lactation, known or suspected allergy to ibuprofen or beta-lactam antibiotics, carious or non-impacted third molars, pericoronitis, or patients in whom excessive technical difficulty was expected
	Age: mean 22 years, range 18 to 46 years
	Group A: randomised 44, analysed 39
	Group B: randomised 45, analysed 40
	Group C: randomised 45, analysed 44

Interventions	**Comparison: preoperative versus postoperative amoxicillin versus placebo**
	Group A: amoxicillin 500 mg 4 times 2 hours preoperatively plus 15 placebo tablets (taken 3 times daily for 5 days)
	Group B: 4 placebo tablets 2 hours preoperatively plus 15 placebo tablets (taken 3 times daily for 5 days)
	Group C: 4 placebo tablets 2 hours preoperatively plus 15 amoxicillin 500 mg (taken 3 times daily for 5 days)

Outcomes	Intraoral swelling, maximal mouth opening, pain (100-point VAS), dysphagia, fever, purulent wound discharge, alveolar osteitis (dry socket), side effects of treatment at 7 days postoperatively

Notes	All procedures were performed by the same surgeon.
	Additional information supplied by author in response to email request.

Risk of bias		

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a random alpha-numeric code"

López-Cedrún 2011 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "at surgery, the surgeon was provided with a set of opaque, sealed envelopes containing the drug code for every patient. Whenever a patient fulfilled the inclusion criteria and gave informed consent, an envelope was opened and the patient was provided with the tablet pack, which matched the drug number"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	High risk	11/134 (8%) participants were excluded from the analysis. 3, 0, 1 participants were excluded from preoperative, postoperative, and placebo groups due to technical difficulty of the procedure, and 2, 1, 4 due to inadequate follow-up. Given the low event rate for infection, it is probable that attrition introduced a bias to the outcome.
Selective reporting (reporting bias)	Low risk	All planned outcomes reported.
Other bias	Unclear risk	Statistically significant difference in mean operating time between pre- and postoperative antibiotic groups

MacGregor 1980

Study characteristics	
Methods	Study design: RCT where participants were paired based on number of lower molars extracted
	Conducted in: UK
	Number of centres: 1
	Recruitment period: unspecified
	Funding: unspecified
Participants	Inclusion criteria: "Caucasian" (understood to be white) participants requiring removal of 1 or 2 mandibular third molars under endotracheal anaesthesia. M3 had to be fully developed with an identifiable occlusal plane.
	Exclusion criteria: people who wear artificial dentures, who could not attend fourth day appointment, those whose operation had "undue haemorrhage", or who required antibiotics for other reasons (e.g. endocarditis).
	Age: unspecified
	Number randomised: unspecified
	Number evaluated: unspecified
Interventions	**Comparison: preoperative penicillin versus placebo**
	Group A: benzyl penicillin 300 mg + procaine penicillin 300 mg intramuscular 30 min preoperatively

MacGregor 1980 *(Continued)*

Group B: placebo injection intramuscular 30 min preoperatively

Procedures performed by 2 surgeons with attempts to standardise methods.

Outcomes	Pain, swelling, and trismus on day 4 in graphs only
Notes	This study was only included in qualitative analysis because it was not possible to extract data for quantitative analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (both participants and surgeons)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind (both participants and surgeons)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers of participants allocated to treatment and assessed on day 4 not stated.
Selective reporting (reporting bias)	Low risk	All planned outcomes reported.
Other bias	Low risk	No other sources of bias identified.

Milani 2015

Study characteristics

Methods	Study design: 3-arm RCT
	Conducted in: Brazil
	Number of centres: 1
	Recruitment period: between January 2011 and January 2012
	Funding source: unspecified
Participants	Inclusion criteria: only healthy people (ASA classification I), both males and females, aged between 18 and 30 years, for whom the extraction of impacted lower third molars was indicated (classification 3C, Pell and Gregory, 1933), with systolic blood pressure ≤ 140 mmHg and diastolic blood pressure ≤ 90 mmHg, heart rate of 70 ± 20 beats/min, and mean body temperature of 36 to 37 °C.
	Exclusion criteria: people who had used antibiotics or anti-inflammatory medications and antiseptic mouthwash in the previous 2 months, those who were pregnant or breastfeeding, smokers, those who

used contraceptives, those with allergies to the drugs used in the study, those with local or systemic clinical signs of infection/inflammation on the day of surgery, and those with injury or radiolucent images in the third molar region. Women were asked as to the day of their menstrual cycle and excluded from the study if they were on day 14 (greatest sensitivity to pain).

Age: 23 +/- 4.3 years

Group A: randomised 31, analysed 30

Group B: randomised 32, analysed 30

Group B: randomised 20, analysed 20

Interventions	**Comparison: pre- and postoperative amoxicillin versus preoperative amoxicillin versus placebo**
	Group A: amoxicillin 1 g 1 hour before surgery plus 500 mg 3 times a day for 7 days postoperatively
	Group B: amoxicillin 1 g 1 hour before surgery plus placebo 3 times a day for 7 days postoperatively
	Group C: placebo 1 hour before surgery plus placebo 3 times a day for 7 days postoperatively
	Participants were instructed to take the analgesic only for pain in the postoperative period (mild pain: 40 drops Lisador 6/6 h; persistent pain: 30 mg Tylex (codeine + paracetamol) 6/6 h). In cases of postoperative infection, the antibiotic or placebo was replaced with clindamycin 300 mg 8/8 h for 7 days, and the participant was withdrawn from the study and treated as required.
Outcomes	Local infection, evaluated dichotomously.
	Postoperative pain, evaluated using a 10-centimetre VAS (0 - no pain, 10 - highest imaginable pain).
	Mouth opening, measured with a digital caliper (interincisal distance between tooth #11 and tooth #41 in mm), and oedema was evaluated by traguslabial commissure and tragus-midline measures using dental floss and transferred to a millimetre ruler
	Dysphagia was scored as follows: difficulty ingesting liquid food (score 1), difficulty eating solids (score 2), and absence of dysphagia (score 0).
	Lymphadenopathy was evaluated by submandibular lymph node palpation using a dichotomous parameter (presence: 1; absence: 0).
	Abnormal temperature, when ≥ 37 °C or when temperature changed ≥ 1.5 °C compared with the baseline measurement.
	Adverse events (number of events).
Notes	Apart from fever and adverse events, the study was not included in the quantitative analysis as data extraction was not possible for the other outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a researcher not connected with the present study generated 80 blocks (www.randomizer.org) with 3 random numbers in each block (corresponding to the 3 drug regimens administered to patients)"
Allocation concealment (selection bias)	Low risk	Quote: "manila envelopes were labelled with codes 1–80 and contained a paper with the corresponding group number (1, 2, or 3)"
Blinding of participants and personnel (performance bias)	Low risk	Quote "surgeon, researcher, and patient did not know the content of the envelope or the corresponding drug. Secrecy was maintained until the end of the statistical analysis"

Milani 2015 *(Continued)*

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "surgeon, researcher, and patient did not know the content of the envelope or the corresponding drug. Secrecy was maintained until the end of the statistical analysis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants lost during the study, 1 from Group A and 2 from Group B. Due to the very low and balanced number of participants lost to follow-up, it is probable that this attrition did not represent a bias. In addition, reasons for leaving the trial were reported.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.
Other bias	Low risk	No other sources of bias identified.

Mitchell 1986

Study characteristics

Methods	Study design: parallel-group RCT
	Conducted in: UK
	Number of centres: 1
	Recruitment period: unspecified
Participants	Inclusion criteria: aged 18 to 30 years, attending hospital for removal of 1 or more third molars
	Exclusion criteria: those with a significant medical history or acute infection
	Age: mean 24 years, range 17 to 33 years
	Group A: randomised 25, analysed 25
	Group B: randomised 25, analysed 25
Interventions	**Comparison: preoperative tinidazole versus placebo**
	Group A: tinidazole 500 mg orally 12 hours preoperatively
	Group B: placebo oral 12 hours preoperatively
	All participants had ibuprofen as required whilst in hospital and access to analgesics as required after discharge.
Outcomes	Local infection in the 7 days following the intervention
Notes	4 surgeons conducted the extractions, using a standardised technique.
	1 clinician blinded to intervention assessed all participants both pre- and postoperatively.

Risk of bias

Bias	Authors' judgement	Support for judgement

Cochrane
Library

Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

Mitchell 1986 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "allocated in accordance with a pre-determined randomisation code during pre-operative assessment"
Allocation concealment (selection bias)	Low risk	Quote: "drugs were individually packaged and allocated"; assumed allocation occurred at the pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants included in the outcome assessment.
Selective reporting (reporting bias)	High risk	Dry socket and normal healing described in the Methods section, but not reported in the Results.
Other bias	Low risk	No other sources of bias identified.

Pasupathy 2011

Study characteristics

Methods	Study design: RCT
	Conducted in: India
	Number of centres: 1
	Recruitment period: unspecified
	Funding source: unspecified
Participants	Inclusion criteria: people with mandibular mesioangularly impacted third molars requiring extraction
	Exclusion criteria: people with infections (space infections, acute pericoronitis), medically compromised, pregnant, allergic to either penicillin or metronidazole, who have taken antibiotics in the 2 months prior to surgery
	Age: mean 29 years, range 18 to 48 years
	Group A: randomised 31, analysed unclear
	Group B: randomised 29, analysed unclear
	Group C: randomised 29, analysed unclear
	9 participants were lost at follow-up overall.
Interventions	**Comparison: preoperative amoxicillin versus preoperative metronidazole versus placebo**
	Group A: amoxicillin 1 g orally 1 hour prior to surgery
	Group B: metronidazole 800 mg orally 1 hour prior to surgery

Pasupathy 2011 *(Continued)*

	Group C: placebo
	All participants received ibuprofen 600 mg 3 times daily for pain.
Outcomes	Surgical wound infection, purulent discharge, fever, restricted mouth opening on day 7 postoperatively
Notes	Sample size: reported that estimated required sample size was 107 in each group. Trial recruited ~30 per group. Groups A and B were analysed together.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation table was prepared using a software program and a random allocating number was given to each patient"
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelopes with the allotted number were used and were dispensed by 1 of our post graduate trainees throughout the study according to the allotted randomization number"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blind – neither the participant nor the surgeon nor the outcome evaluator was aware of the allocated treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Triple-blind – neither the participant nor the surgeon nor the outcome evaluator was aware of the allocated treatment.
Incomplete outcome data (attrition bias) All outcomes	High risk	9/98 (9%) of randomised participants excluded from the analysis, due to either not returning for follow-up (n = 8) or use of antibiotic (n = 1). The allocated treatment groups for these 9 participants are not described. Given the low event rate, this attrition is likely to have introduced bias.
Selective reporting (reporting bias)	Unclear risk	Outcomes were not clearly reported in the Material and Methods section.
Other bias	Low risk	No other sources of bias identified.

Ritzau 1992

Study characteristics

Methods	Study design: RCT
	Conducted in: Denmark
	Number of centres: 2
	Recruitment period: between October 1987 and November 1988
	Funding source: unspecified
Participants	Inclusion criteria: healthy participants scheduled for surgical removal of an impacted (partially or totally) mandibular third molar
	Exclusion criteria: any medical condition that might interfere with the study, acute pericoronitis, participants who had taken antibiotics within 48 hours before surgery were also excluded

Ritzau 1992 *(Continued)*

	Age: unspecified
	A total of 312 participants were randomised into 2 groups.
	Group A: randomised unclear, analysed 135
	Group B: randomised unclear, analysed 135
	42 participants did not complete the study: 4 did not comply with the protocol; 4 withdrew voluntarily; 1 had intercurrent disease; 11 were lost to follow-up for various reasons; 22 did not present for surgery after having been enrolled.
Interventions	**Comparison: preoperative metronidazole versus placebo**
	Group A: 1000 mg metronidazole no later than 30 min before surgery
	Group B: placebo no later than 30 min before surgery
Outcomes	Follow-up examination was scheduled for a week after surgery when sutures were to be removed. Alveolitis sicca dolorosa (dry socket) was diagnosed when 2 criteria were simultaneously present: 1) severe pain irradiating from the empty socket towards the ipsilateral ear, and 2) disintegration (partial or total) of the socket coagulum.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random sequence ... generated by a computerized program"
Allocation concealment (selection bias)	Low risk	Quote: "the code was unknown to the investigators until the termination of collection of clinical data"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" and "metronidazole and placebo were manufactured in the shape of pills of identical size, shape, weight, and colour, packed and code numbered"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind" and "metronidazole and placebo were manufactured in the shape of pills of identical size, shape, weight, and colour, packed and code numbered"
Incomplete outcome data (attrition bias) All outcomes	High risk	22/312 randomised participants did not have surgery. 20/290 (7%) participants who did undergo surgery were excluded from the outcome evaluation, but allocated treatment was not stated. No specific ITT approach is reported, attrition rate is higher than event rate (4.8%), and bias in these results is considered likely.
Selective reporting (reporting bias)	Low risk	All planned outcomes reported.
Other bias	Low risk	No other sources of bias identified.

Sekhar 2001 *(Continued)*

Study characteristics

Methods	Study design: RCT
	Conducted in: India
	Number of centres: 1
	Recruitment period: unspecified
	Funding source: unspecified
Participants	Inclusion criteria: aged 19 to 36 requiring removal of lower wisdom teeth under local anaesthesia.
	Exclusion criteria: pre-existing abscess or cellulitis, acute pericoronitis, pre-existing conditions associated with third molars, xerostomia. Those requiring antibiotic prophylaxis for other reasons, immunocompromised patients, pregnancy, diabetes, cancer, or renal failure, and those who had received antibiotics in 2 weeks prior to start of study.
	Age: mean 30 years
	Group A: randomised 53, analysed 44
	Group B: randomised 61, analysed 47
	Group C: randomised 37, analysed 34
Interventions	**Comparison: preoperative versus postoperative metronidazole versus placebo**
	Group A: metronidazole 1 g 1 hour preoperatively
	Group B: metronidazole 400 mg 8 hourly for 5 days
	Group C: placebo (frequency of administration not specified)
	All participants had a prescription for ibuprofen 400 mg to be taken as required for pain relief.
Outcomes	Pain (4-point scale) measured on days 2 and 6 postoperatively, interincisal mouth opening (mm), whether there was purulent discharge from wound, dry socket on day 6, swelling
Notes	Surgeons performing the extractions were either consultants, postgraduate trainees, or house officers. The report does not indicate whether placebo tablets were provided for pre- and postprophylaxis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned using prepared randomizations in sealed envelopes". Method of sequence generation not described.
Allocation concealment (selection bias)	Low risk	Allocation concealed in sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind, but dosing schedule different in each group. Outcome assessor was blinded to allocated treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind, but dosing schedule different in each group. Outcome assessor was blinded to allocated treatment.

Sekhar 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	26/151 (17%) (9, 14, and 3 from groups A, B, and C) of those randomised were excluded because they did not return for follow-up evaluation. Excluded participants were more likely to have had bone removed and had longer mean operating times. Given the low event rate, this attrition could have resulted in biased outcome estimates.
Selective reporting (reporting bias)	High risk	Dry socket and seeking medical help postoperatively were not reported in the results.
Other bias	Unclear risk	Percentage of participants in 2 times daily metronidazole group who had bone removed appeared to be significantly lower compared to other groups.

Sixou 2012

Study characteristics	
Methods	Study design: RCT
	Conducted in: France
	Number of centres: 11
	Recruitment period: between September 2000 and September 2005
	Funding source: unspecified
Participants	Inclusion criteria: good health, need complex oral surgery with an estimated intervention length of less than 90 minutes, including complex avulsion, bone or soft tissue surgery, implant, dental re-implantation, or orthodontic disimpaction surgery
	Exclusion criteria: any acute oral infection before surgery, taking antibiotics in the prior 30 days, using any medication which could interact with amoxicillin, allergies, susceptibility to infection (general conditions, e.g. diabetes, or local lesions, e.g. those caused by radiotherapy, etc.) and previous postoperative infections, pregnant women, nursing mothers, participants presenting with renal or hepatic insufficiency, and those incapable of giving their informed consent
	Age: 26.3 years
	Group 1: randomised 142, analysed 126
	Group 2: randomised 141, analysed 124
Interventions	**Comparison: preoperative antibiotic versus placebo**
	Group 1: amoxicillin 3 g (3 sachets) 1 hour before surgery
	Group 2: placebo 3 g (3 sachets) 1 hour before surgery
	Participants were instructed to take postoperative medications by the oral surgeon.
Outcomes	Local infection, evaluated dichotomously (defined as the contemporaneous presence of at least 4 signs amongst tumefaction, redness, cervical or submandibular lymphadenopathy, pus, trismus, fever, and pain)
	Perioperative complications
	Postoperative pain, evaluated dichotomously
	Number of drugs taken

Sixou 2012 *(Continued)*

	Adverse events (number of events)
Notes	This study enrolled people undergoing different kinds of oral surgery procedures, including extractions, surgery of soft tissues, and dental implants, thus we included this study only in qualitative analysis because it was not possible to stratify data according to the kind of intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a blocked, computer-generated randomization list"
Allocation concealment (selection bias)	Low risk	Quote: "the randomization codes linking allocation to study number were held only by the Independent Medical Research Council Clinical Trials Unit"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the medications were blinded, [...] and packed by an authorized company"; "the randomization codes linking allocation to study number were held only by the Independent Medical Research Council Clinical Trials Unit"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the medications were blinded, [...] and packed by an authorized company"; "the randomization codes linking allocation to study number were held only by the Independent Medical Research Council Clinical Trials Unit"
Incomplete outcome data (attrition bias) All outcomes	Low risk	33 participants lost during the study: 16 from Group 1 (amoxicillin) and 17 from Group 2 (placebo). Due to the relatively low and balanced number of participants lost to follow-up, it is probable that this attrition did not represent a bias.
Selective reporting (reporting bias)	High risk	Some of the outcomes mentioned in Material and Methods section are not reported in the Results section (lymphadenopathy, pus, trismus, fever).
Other bias	Low risk	No other sources of bias identified.

ASA = American Society of Anesthesiologists; ITT = intention-to-treat; RCT = randomised controlled trial; VAS = visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abu-Mowais 1990	Not double-blind
Adde 2012	Not double-blind, not placebo-controlled
Arora 2014	Not placebo-controlled
Ataoglu 2008	Not double-blind
Bargnesi 1985	Study of antibiotics used in conjunction with a range of small dental surgical procedures including but not limited to tooth extractions
Barone 2017	Not placebo-controlled
Busa 2014	Not placebo-controlled

Study	Reason for exclusion
Curran 1974	Described as double-blind, but control group received no treatment. Participants not blinded to treatment, and asked not to inform outcome assessors.
Delilbasi 2004	Not double-blind
de Moura 2011	Washout period 4 weeks (translated from Spanish)
Foy 2004	Not double-blind
Fridrich 1990	Not randomised or quasi-randomised
Graziani 2005	Not double-blind
Grossi 2007	Not double-blind
Head 1984	Bacteraemia outcomes only
Krekmanov 1980	Not double-blind
Krekmanov 1981	Not double-blind
Krekmanov 1986	Not double-blind
Laird 1972	Compares 2 antibiotic regimens
Limeres 2009	Compares 2 antibiotic regimens
Lombardia Garcia 1987	Not double-blind
Lopes 2011	Not double-blind
Luaces-Rey 2010	Compares 2 antibiotic regimens
Lyall 1991	Not double-blind
MacGregor 1973	Topical antibiotic
Milani 2012	Not placebo-controlled
Mitchell 1987	No blinding described.
Monaco 1999	Not double-blind
Monaco 2009	Not double-blind
Olusanya 2011	Compares 2 antibiotic regimens
Osborn 1979	From translator: "it is clear that this study is double blinded but it is unclear how participants were allocated to treatment groups. Random not mentioned"
Poeschl 2004	Not double-blind
Reekie 2006	Topical antibiotic therapy
Rood 1979	Not randomised

Study	Reason for exclusion
Samsudin 1994	Not randomised or quasi-randomised and not double-blind
Siddiqi 2010	Washout period only 3 weeks (communication with author)
Stavropoulos 2006	Authors considered only topical antibiotic therapy.
Sulejmanagić 2005	Not randomised or quasi-randomised and not double-blind
Swanson 1989	Topical antibiotic therapy
Uluibau 2005	Not double-blind
Walkow 1995	Abstract only, no mention of blinding and no subsequent trial report found
Xue 2015	Washout period 10 to 14 days
Yoshii 2002	No blinding described.

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2019/12/022342

Study name	Comparative evaluation of necessity of antibiotic administration following dental extraction among population of age group 30 - 60 years - triple blinded randomized control trial
Methods	Randomised, parallel-group, multiple-arm trial method of generating randomisation sequence: coin toss, lottery, toss of dice, shuffling cards, etc. Method of allocation concealment: sequentially numbered, sealed, opaque envelopes. Blinding and masking: participant, investigator, and outcome assessor blinded
Participants	Inclusion criteria: patients aged 30 to 60 years old who are willing to participate in this study
	Exclusion criteria: medically compromised, females who are pregnant or lactating and those women during menstruation period (disturbed fibrinolytic activity), and patients who are known to be hypersensitive to the test drugs used in this study, and tooth with abscess and cyst and patients taking antibiotics on preoperative 5 days for any reason
Interventions	Intervention 1: clindamycin group: clindamycin drug as a mouthwash postextraction, 150 mg in 100 mL of water, 3 times a day
	Control intervention 1: amoxicillin group: amoxicillin drug systemically postextraction as a gold standard prescribing style, 500 mg, 3 times a day
	Control intervention 2: no antibiotic group: antibiotic is not prescribed postextraction
Outcomes	Primary outcome: the need for antibiotic administration during postextraction period will be limited when there is no significant difference between healing pattern for all 3 comparing groups. Time point: 3rd day, 7th day, and 14th day
	Secondary outcome: healing comparison between 3 groups. Time point: 3rd day, 7th day, 14th day
Starting date	16 December 2019
Contact information	Sasidharan Sivakumar, Department of Public Health Dentistry, Best Dental Science College, 625104 Madurai, Tamil Nadu, India. drumeshk@gmail.com

CTRI/2019/12/022342 *(Continued)*

Notes	

EudraCT 2017-004986-28

Study name	Effect of systemic antibiotic therapy on postoperative complications in patients undergoing wisdom teeth removal surgery. A double-blind, randomised, placebo-controlled trial - AMOXI
Methods	Controlled: yes
	Randomised: yes
	Open: no
	Single-blind: no
	Double-blind: yes
	Parallel group: yes
	Cross-over: yes
	Other: yes
	Other trial design description: split-mouth design
	If controlled, specify comparator, other medicinal product: no
	Placebo: yes
	Other: no
	Number of treatment arms in the trial: 2
Participants	Inclusion criteria:
	• medically healthy (age >= 16 years) • symptom-free • bilaterally located third molars • no allergies/intolerances against the investigational product/placebo
	Exclusion criteria:
	• general contraindications to wisdom tooth extraction surgery • (former) heavy smoking • use of antibiotics within the last 3 months or patients requiring antibiotic treatment prior to surgery • (planned) pregnancy/lactating
Interventions	Amoxicillin (Amoxilan) 1000 mg tablets
Outcomes	Main objective: to evaluate whether the perioperative usage of antibiotics is effective in reducing postoperative complications compared to placebo, in patients undergoing wisdom teeth removal.
	Secondary endpoint(s): occurrence of pain, bleeding, swelling
Starting date	25 March 2019
Contact information	Prof PD DDr. Michael Payer, Billrothgasse 4 8010 Graz Austria

mi.payer@medunigraz.at

Notes	

DATA AND ANALYSES

Comparison 1.   Antibiotic versus placebo

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1.1 Postsurgical infectious com- plications (6th to 7th day)	12	1728	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.19, 0.64]
1.1.1 Preoperative prophylaxis	7	500	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.16, 0.62]
1.1.2 Postoperative prophylaxis	5	872	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.05, 0.80]
1.1.3 Pre- and postoperative pro- phylaxis	3	356	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.38, 2.52]
1.2 Pain (dichotomous on 6th to 7th day)	3	675	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.31, 1.12]
1.2.1 Preoperative prophylaxis	1	61	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.57, 2.12]
1.2.2 Postoperative prophylaxis	2	554	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.15, 1.52]
1.2.3 Pre- and postoperative pro- phylaxis	1	60	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.13, 0.98]
1.3 Pain score (VAS 0 to 10 cm where 0 = no pain) 7th day	4	422	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.59, 0.07]
1.3.1 Preoperative prophylaxis	2	106	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.44, 0.24]
1.3.2 Postoperative prophylaxis	1	64	Mean Difference (IV, Random, 95% CI)	0.10 [-0.22, 0.42]
1.3.3 Pre- and postoperative pro- phylaxis	3	252	Mean Difference (IV, Random, 95% CI)	-0.75 [-1.22, -0.28]
1.4 Fever (6th to 7th day)	4	475	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.24, 1.79]
1.4.1 Preoperative prophylaxis	2	139	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4.2 Postoperative prophylaxis	3	296	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.24, 1.79]
1.4.3 Pre- and postoperative prophylaxis	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.5 Swelling (7th day)	4	452	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.50, 1.27]
1.5.1 Preoperative prophylaxis	3	165	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.69, 1.83]
1.5.2 Postoperative prophylaxis	2	128	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.35, 1.34]
1.5.3 Pre- and postoperative prophylaxis	2	159	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.10, 2.98]
1.6 Trismus (7th day)	3	199	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.42, 1.41]
1.6.1 Preoperative prophylaxis	3	158	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.36, 1.46]
1.6.2 Pre- and postoperative prophylaxis	1	41	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.27, 3.14]
1.7 Dry socket (6th to 7th day)	13	1882	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.45, 0.97]
1.7.1 Preoperative prophylaxis	7	724	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.42, 1.34]
1.7.2 Postoperative prophylaxis	3	704	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.12, 5.54]
1.7.3 Pre- and postoperative prophylaxis	5	454	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.28, 0.90]
1.8 Adverse events (6th to 7th day)	8	1277	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.81, 2.64]
1.8.1 Preoperative prophylaxis	5	317	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.49, 1.90]
1.8.2 Postoperative prophylaxis	3	666	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.24, 6.51]
1.8.3 Pre- and postoperative prophylaxis	4	294	Risk Ratio (M-H, Random, 95% CI)	2.44 [0.95, 6.24]

Analysis 1.1. Comparison 1: Antibiotic versus placebo, Outcome 1: Postsurgical infectious complications (6th to 7th day)

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.1.1 Preoperative prophylaxis								
Bortoluzzi 2013	0	12	0	12		Not estimable		? ? + + + + +
Halpern 2007	0	59	5	59	4.1%	0.09 [0.01 , 1.61]		? + + + + + +
Lacasa 2007	4	68	3	31	11.9%	0.61 [0.14 , 2.55]		? ? + + − − ?
López-Cedrún 2011	0	39	3	20	4.0%	0.07 [0.00 , 1.38]		+ + + + − + ?
Mitchell 1986	4	25	14	25	18.3%	0.29 [0.11 , 0.75]		+ + + + + − +
Pasupathy 2011	2	60	3	29	9.2%	0.32 [0.06 , 1.82]		+ + + + − ? +
Sekhar 2001	1	44	0	17	3.4%	1.20 [0.05 , 28.10]		? + + + − − ?
Subtotal (95% CI)		**307**		**193**	**50.7%**	**0.32 [0.16 , 0.62]**		
Total events:	11		28					
Heterogeneity: Tau² = 0.00; Chi² = 3.28, df = 5 (P = 0.66); I² = 0%								
Test for overall effect: Z = 3.34 (P = 0.0008)								
1.1.2 Postoperative prophylaxis								
Arteagoitia 2005	2	261	22	233	11.8%	0.08 [0.02 , 0.34]		+ + + + + − +
Gbotolorun 2016	1	75	0	75	3.4%	3.00 [0.12 , 72.49]		+ + + + + + +
Lacasa 2007	2	69	3	31	9.1%	0.30 [0.05 , 1.70]		? ? + + − − ?
López-Cedrún 2011	0	44	2	20	3.8%	0.09 [0.00 , 1.86]		+ + + + − + ?
Sekhar 2001	0	47	0	17		Not estimable		? + + + − − ?
Subtotal (95% CI)		**496**		**376**	**28.1%**	**0.21 [0.05 , 0.80]**		
Total events:	5		27					
Heterogeneity: Tau² = 0.68; Chi² = 4.75, df = 3 (P = 0.19); I² = 37%								
Test for overall effect: Z = 2.29 (P = 0.02)								
1.1.3 Pre- and postoperative prophylaxis								
Arteagoitia 2015	0	60	1	58	3.4%	0.32 [0.01 , 7.76]		+ ? + + + + +
Happonen 1990	11	91	5	45	17.8%	1.09 [0.40 , 2.94]		? ? + + − − +
Leon Arcila 2001	0	49	0	53		Not estimable		+ + + + + + +
Subtotal (95% CI)		**200**		**156**	**21.1%**	**0.98 [0.38 , 2.52]**		
Total events:	11		6					
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%								
Test for overall effect: Z = 0.05 (P = 0.96)								
Total (95% CI)		**1003**		**725**	**100.0%**	**0.34 [0.19 , 0.64]**		
Total events:	27		61					
Heterogeneity: Tau² = 0.30; Chi² = 15.29, df = 11 (P = 0.17); I² = 28%								
Test for overall effect: Z = 3.39 (P = 0.0007)								
Test for subgroup differences: Chi² = 4.70, df = 2 (P = 0.10), I² = 57.4%								

```
0.001    0.1      1      10     1000
   Favours antibiotic   Favours placebo
```

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 1.2. Comparison 1: Antibiotic versus placebo, Outcome 2: Pain (dichotomous on 6th to 7th day)

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.2.1 Preoperative prophylaxis								
Sekhar 2001	20	44	7	17	29.8%	1.10 [0.57 , 2.12]		? + + + − − ?
Subtotal (95% CI)		**44**		**17**	**29.8%**	**1.10 [0.57 , 2.12]**		
Total events:	20		7					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.77)								
1.2.2 Postoperative prophylaxis								
Arteagoitia 2005	4	259	14	231	19.0%	0.25 [0.09 , 0.76]		+ + + + + − +
Sekhar 2001	17	47	8	17	30.5%	0.77 [0.41 , 1.44]		? + + + − − ?
Subtotal (95% CI)		**306**		**248**	**49.5%**	**0.48 [0.15 , 1.52]**		
Total events:	21		22					
Heterogeneity: Tau² = 0.50; Chi² = 3.39, df = 1 (P = 0.07); I² = 71%								
Test for overall effect: Z = 1.25 (P = 0.21)								
1.2.3 Pre- and postoperative prophylaxis								
Bystedt 1981	5	40	7	20	20.7%	0.36 [0.13 , 0.98]		? ? + + + − +
Subtotal (95% CI)		**40**		**20**	**20.7%**	**0.36 [0.13 , 0.98]**		
Total events:	5		7					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.99 (P = 0.05)								
Total (95% CI)		**390**		**285**	**100.0%**	**0.59 [0.31 , 1.12]**		
Total events:	46		36					
Heterogeneity: Tau² = 0.24; Chi² = 7.35, df = 3 (P = 0.06); I² = 59%								
Test for overall effect: Z = 1.61 (P = 0.11)								
Test for subgroup differences: Chi² = 3.95, df = 2 (P = 0.14), I² = 49.4%								

0.01   0.1   1   10   100
Favours antibiotic   Favours placebo

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 1.3. Comparison 1: Antibiotic versus placebo, Outcome 3: Pain score (VAS 0 to 10 cm where 0 = no pain) 7th day

Study or Subgroup	Antibiotic Mean	Antibiotic SD	Antibiotic Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Preoperative prophylaxis								
Kaczmarzyk 2007	0.95	2.4	31	1.01	1.9	14	5.5%	-0.06 [-1.37 , 1.25]
Sekhar 2001	2.4	0.7	44	2.5	0.6	17	28.9%	-0.10 [-0.45 , 0.25]
Subtotal (95% CI)			**75**			**31**	**34.4%**	**-0.10 [-0.44 , 0.24]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%								
Test for overall effect: Z = 0.56 (P = 0.58)								
1.3.2 Postoperative prophylaxis								
Sekhar 2001	2.6	0.5	47	2.5	0.6	17	30.7%	0.10 [-0.22 , 0.42]
Subtotal (95% CI)			**47**			**17**	**30.7%**	**0.10 [-0.22 , 0.42]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.61 (P = 0.54)								
1.3.3 Pre- and postoperative prophylaxis								
Arteagoitia 2015	1.1	2	59	1.8	2.1	57	13.4%	-0.70 [-1.45 , 0.05]
Barclay 1987	0.63	1.25	45	1.48	2.2	50	14.3%	-0.85 [-1.56 , -0.14]
Kaczmarzyk 2007	0.39	0.98	28	1.01	1.95	13	7.2%	-0.62 [-1.74 , 0.50]
Subtotal (95% CI)			**132**			**120**	**34.9%**	**-0.75 [-1.22 , -0.28]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 2 (P = 0.93); I² = 0%								
Test for overall effect: Z = 3.15 (P = 0.002)								
Total (95% CI)			**254**			**168**	**100.0%**	**-0.26 [-0.59 , 0.07]**
Heterogeneity: Tau² = 0.07; Chi² = 8.94, df = 5 (P = 0.11); I² = 44%								
Test for overall effect: Z = 1.56 (P = 0.12)								
Test for subgroup differences: Chi² = 8.79, df = 2 (P = 0.01), I² = 77.2%								

Favours antibiotic   Favours placebo

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Antibiotic versus placebo, Outcome 4: Fever (6th to 7th day)

Study or Subgroup	Antibiotic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.4.1 Preoperative prophylaxis								
Lacasa 2007	0	68	0	31		Not estimable		? ? + + − − ?
Milani 2015	0	30	0	10		Not estimable		+ + + + + + +
Subtotal (95% CI)		**98**		**41**		**Not estimable**		
Total events:	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
1.4.2 Postoperative prophylaxis								
Bystedt 1981	0	40	0	20		Not estimable		? ? + + + − +
Happonen 1990	8	91	6	45	100.0%	0.66 [0.24 , 1.79]		? ? + + − − +
Lacasa 2007	0	69	0	31		Not estimable		? ? + + − − ?
Subtotal (95% CI)		**200**		**96**	**100.0%**	**0.66 [0.24 , 1.79]**		
Total events:	8		6					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.82 (P = 0.41)								
1.4.3 Pre- and postoperative prophylaxis								
Milani 2015	0	30	0	10		Not estimable		+ + + + + + +
Subtotal (95% CI)		**30**		**10**		**Not estimable**		
Total events:	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)		**328**		**147**	**100.0%**	**0.66 [0.24 , 1.79]**		
Total events:	8		6					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.82 (P = 0.41)								
Test for subgroup differences: Not applicable								

0.01   0.1   1   10   100
Favours antibiotic   Favours placebo

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 1.5. Comparison 1: Antibiotic versus placebo, Outcome 5: Swelling (7th day)

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.5.1 Preoperative prophylaxis								
Kaczmarzyk 2007	9	31	2	14	8.3%	2.03 [0.50 , 8.21]		+ + + + − + +
López-Cedrún 2011	10	39	6	20	15.7%	0.85 [0.36 , 2.01]		+ + + + − + ?
Sekhar 2001	21	44	7	17	20.4%	1.16 [0.61 , 2.21]		? + + + − − ?
Subtotal (95% CI)		**114**		**51**	**44.4%**	**1.13 [0.69 , 1.83]**		
Total events:	40		15					
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 2 (P = 0.57); I² = 0%								
Test for overall effect: Z = 0.48 (P = 0.63)								
1.5.2 Postoperative prophylaxis								
López-Cedrún 2011	13	44	6	20	16.6%	0.98 [0.44 , 2.21]		+ + + + − + ?
Sekhar 2001	11	47	8	17	18.6%	0.50 [0.24 , 1.02]		? + + + − − ?
Subtotal (95% CI)		**91**		**37**	**35.2%**	**0.68 [0.35 , 1.34]**		
Total events:	24		14					
Heterogeneity: Tau² = 0.08; Chi² = 1.54, df = 1 (P = 0.21); I² = 35%								
Test for overall effect: Z = 1.12 (P = 0.26)								
1.5.3 Pre- and postoperative prophylaxis								
Arteagoitia 2015	4	60	16	58	12.6%	0.24 [0.09 , 0.68]		+ ? + + + + +
Kaczmarzyk 2007	6	28	2	13	7.8%	1.39 [0.32 , 5.99]		+ + + + − + +
Subtotal (95% CI)		**88**		**71**	**20.3%**	**0.54 [0.10 , 2.98]**		
Total events:	10		18					
Heterogeneity: Tau² = 1.13; Chi² = 3.71, df = 1 (P = 0.05); I² = 73%								
Test for overall effect: Z = 0.71 (P = 0.48)								
Total (95% CI)		**293**		**159**	**100.0%**	**0.80 [0.50 , 1.27]**		
Total events:	74		47					
Heterogeneity: Tau² = 0.16; Chi² = 10.68, df = 6 (P = 0.10); I² = 44%								
Test for overall effect: Z = 0.94 (P = 0.35)								
Test for subgroup differences: Chi² = 1.80, df = 2 (P = 0.41), I² = 0%								

0.05 0.2 1 5 20
Favours antibiotic   Favours placebo

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 1.6.   Comparison 1: Antibiotic versus placebo, Outcome 6: Trismus (7th day)

Study or Subgroup	Antibiotic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.6.1 Preoperative prophylaxis								
Bortoluzzi 2013	3	12	5	12	26.0%	0.60 [0.18 , 1.97]		? ? + + + + +
Kaczmarzyk 2007	7	31	3	14	25.6%	1.05 [0.32 , 3.49]		+ + + + − + +
Pasupathy 2011	5	60	4	29	23.9%	0.60 [0.18 , 2.08]		+ + + + − ? +
Subtotal (95% CI)		**103**		**55**	**75.4%**	**0.73 [0.36 , 1.46]**		
Total events:	15		12					

Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)

Study or Subgroup	Antibiotic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.6.2 Pre- and postoperative prophylaxis								
Kaczmarzyk 2007	6	28	3	13	24.6%	0.93 [0.27 , 3.14]		+ + + + − + +
Subtotal (95% CI)		**28**		**13**	**24.6%**	**0.93 [0.27 , 3.14]**		
Total events:	6		3					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.91)

Study or Subgroup	Antibiotic	Total	Placebo	Total	Weight	Risk Ratio M-H, Random, 95% CI		
Total (95% CI)		**131**		**68**	**100.0%**	**0.77 [0.42 , 1.41]**		
Total events:	21		15					

Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 3 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%

0.01   0.1   1   10   100
Favours antibiotic   Favours placebo

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
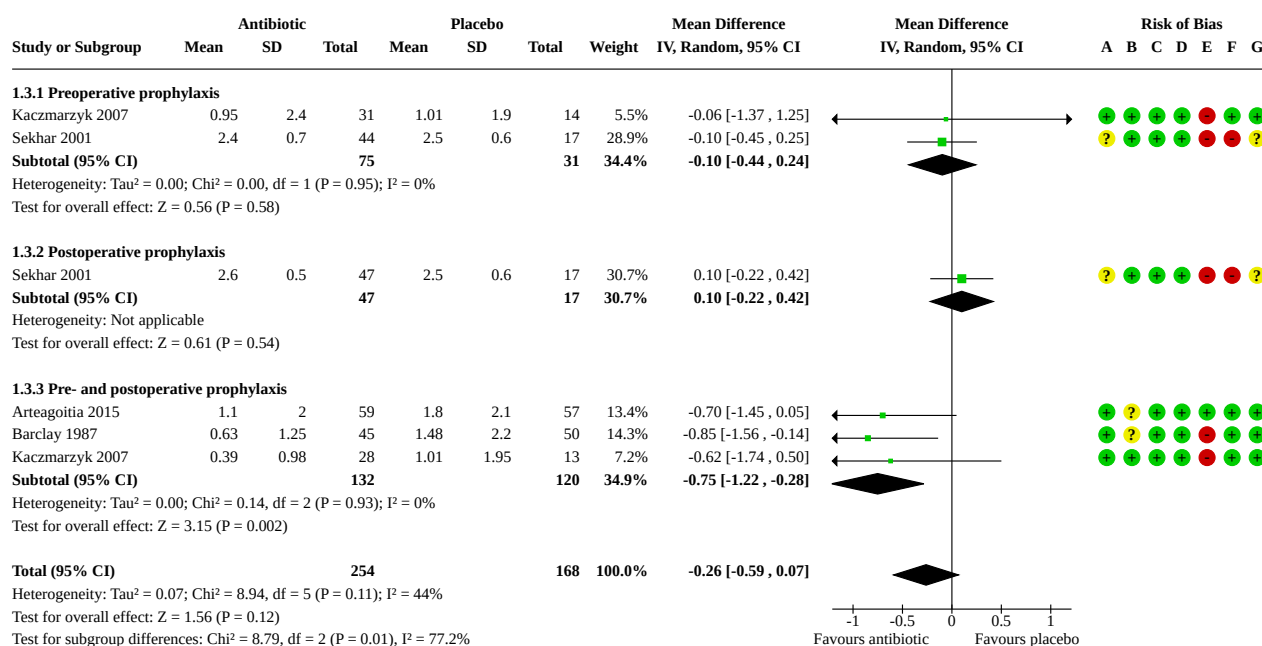(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.7. Comparison 1: Antibiotic versus placebo, Outcome 7: Dry socket (6th to 7th day)

	Antibiotic		Placebo			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**	**A B C D E F G**
1.7.1 Preoperative prophylaxis								
Bergdahl 2004	10	59	13	60	27.0%	0.78 [0.37 , 1.64]		? ? + + + − ?
Bortoluzzi 2013	1	12	1	12	2.1%	1.00 [0.07 , 14.21]		? ? + + + + +
Halpern 2007	0	59	0	59		Not estimable		? + + + + + +
Kaczmarzyk 2007	1	31	2	14	2.8%	0.23 [0.02 , 2.29]		+ + + + − + +
López-Cedrún 2011	0	39	0	20		Not estimable		+ + + + − + ?
Pasupathy 2011	0	60	0	29		Not estimable		+ + + + − ? +
Ritzau 1992	6	135	7	135	13.1%	0.86 [0.30 , 2.48]		+ + + + − + +
Subtotal (95% CI)		**395**		**329**	**45.0%**	**0.75 [0.42 , 1.34]**		
Total events:	18		23					
Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 3 (P = 0.76); I² = 0%								
Test for overall effect: Z = 0.97 (P = 0.33)								
1.7.2 Postoperative prophylaxis								
Arteagoitia 2005	0	259	2	231	1.6%	0.18 [0.01 , 3.70]		+ + + + − + +
Gbotolorun 2016	6	75	4	75	9.9%	1.50 [0.44 , 5.10]		+ + + + + + +
López-Cedrún 2011	0	44	0	20		Not estimable		+ + + + − + ?
Subtotal (95% CI)		**378**		**326**	**11.5%**	**0.82 [0.12 , 5.54]**		
Total events:	6		6					
Heterogeneity: Tau² = 0.95; Chi² = 1.68, df = 1 (P = 0.19); I² = 41%								
Test for overall effect: Z = 0.21 (P = 0.84)								
1.7.3 Pre- and postoperative prophylaxis								
Arteagoitia 2015	0	60	0	58		Not estimable		+ ? + + + + +
Barclay 1987	8	45	17	50	27.3%	0.52 [0.25 , 1.09]		+ + + + − + +
Bystedt 1980	3	80	5	60	7.7%	0.45 [0.11 , 1.81]		? ? + + − + ?
Bystedt 1981	2	40	2	20	4.2%	0.50 [0.08 , 3.29]		? ? + + + + +
Kaczmarzyk 2007	2	28	2	13	4.4%	0.46 [0.07 , 2.94]		+ + + + − + +
Subtotal (95% CI)		**253**		**201**	**43.5%**	**0.50 [0.28 , 0.90]**		
Total events:	15		26					
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 3 (P = 1.00); I² = 0%								
Test for overall effect: Z = 2.32 (P = 0.02)								
Total (95% CI)		**1026**		**856**	**100.0%**	**0.66 [0.45 , 0.97]**		
Total events:	39		55					
Heterogeneity: Tau² = 0.00; Chi² = 4.69, df = 9 (P = 0.86); I² = 0%								
Test for overall effect: Z = 2.12 (P = 0.03)								
Test for subgroup differences: Chi² = 1.03, df = 2 (P = 0.60), I² = 0%								

0.1 0.2 0.5 1 2 5 10
Favours antibiotic   Favours placebo

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

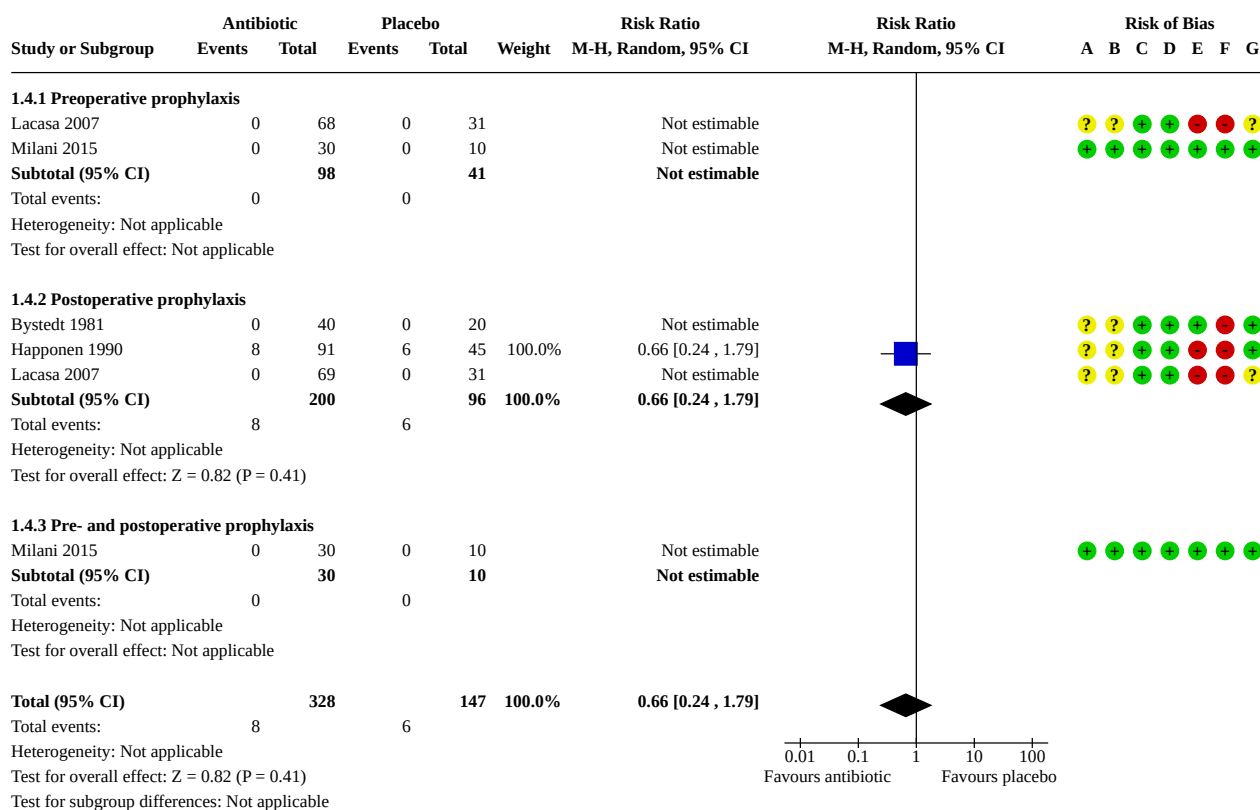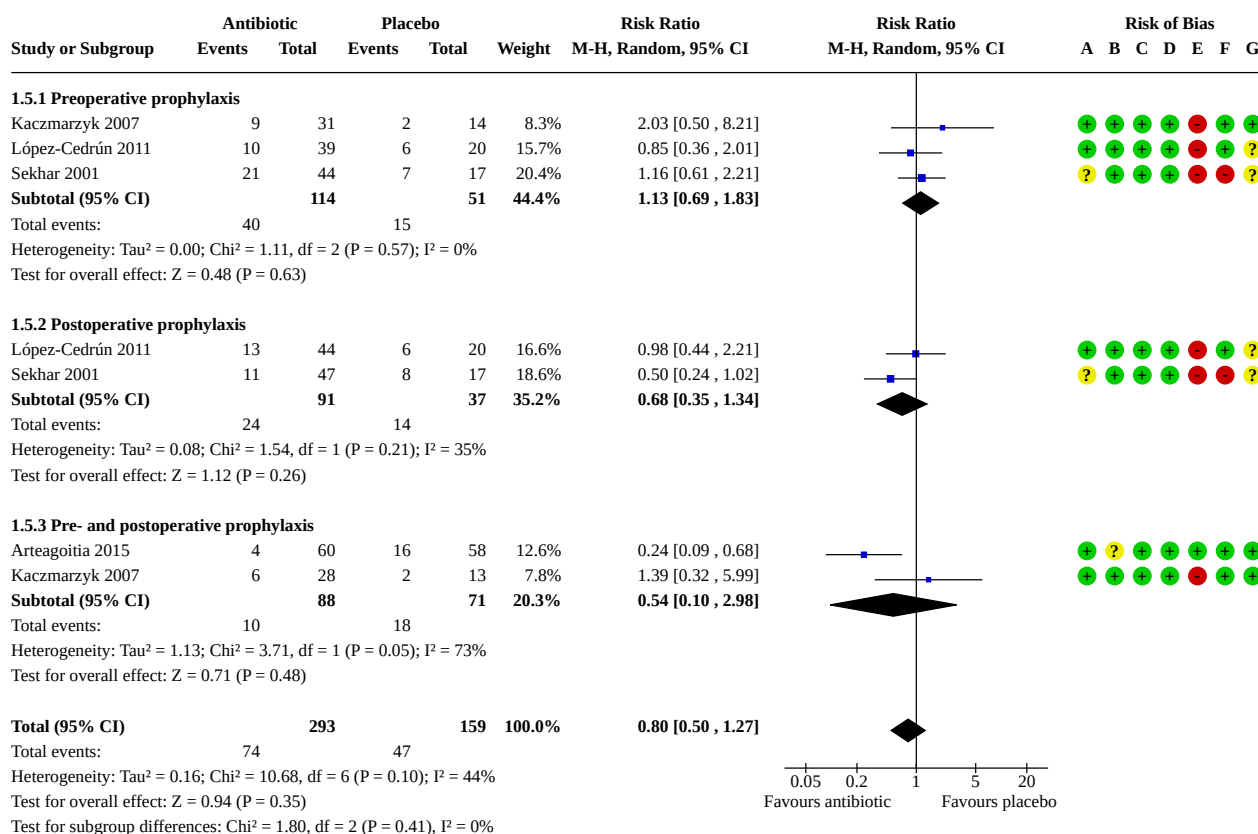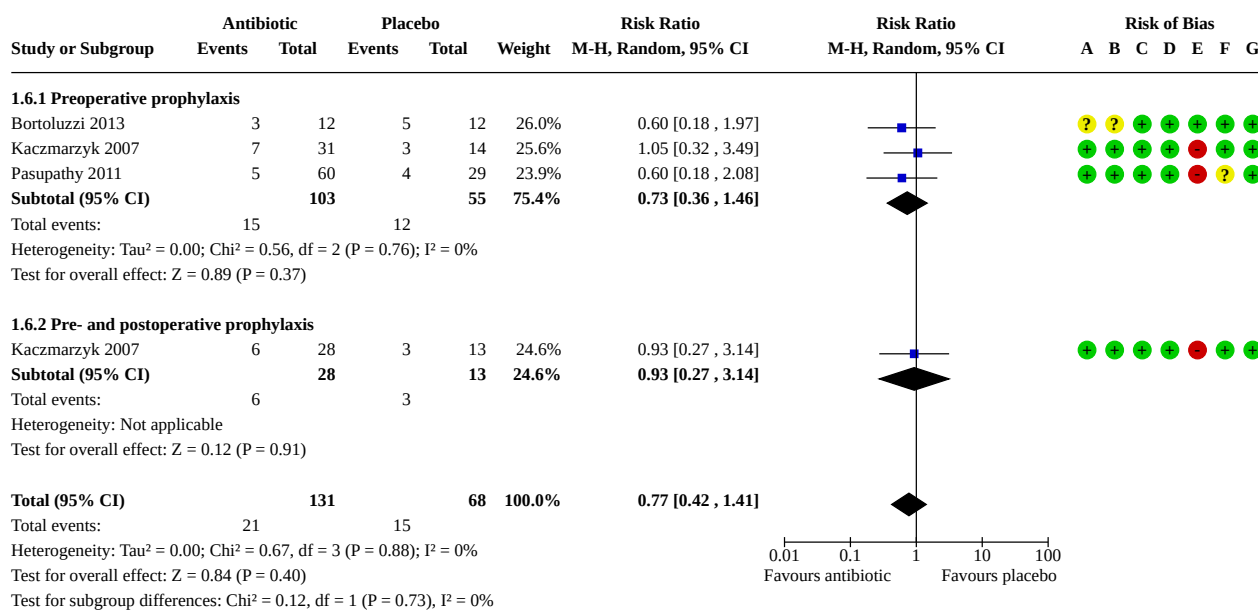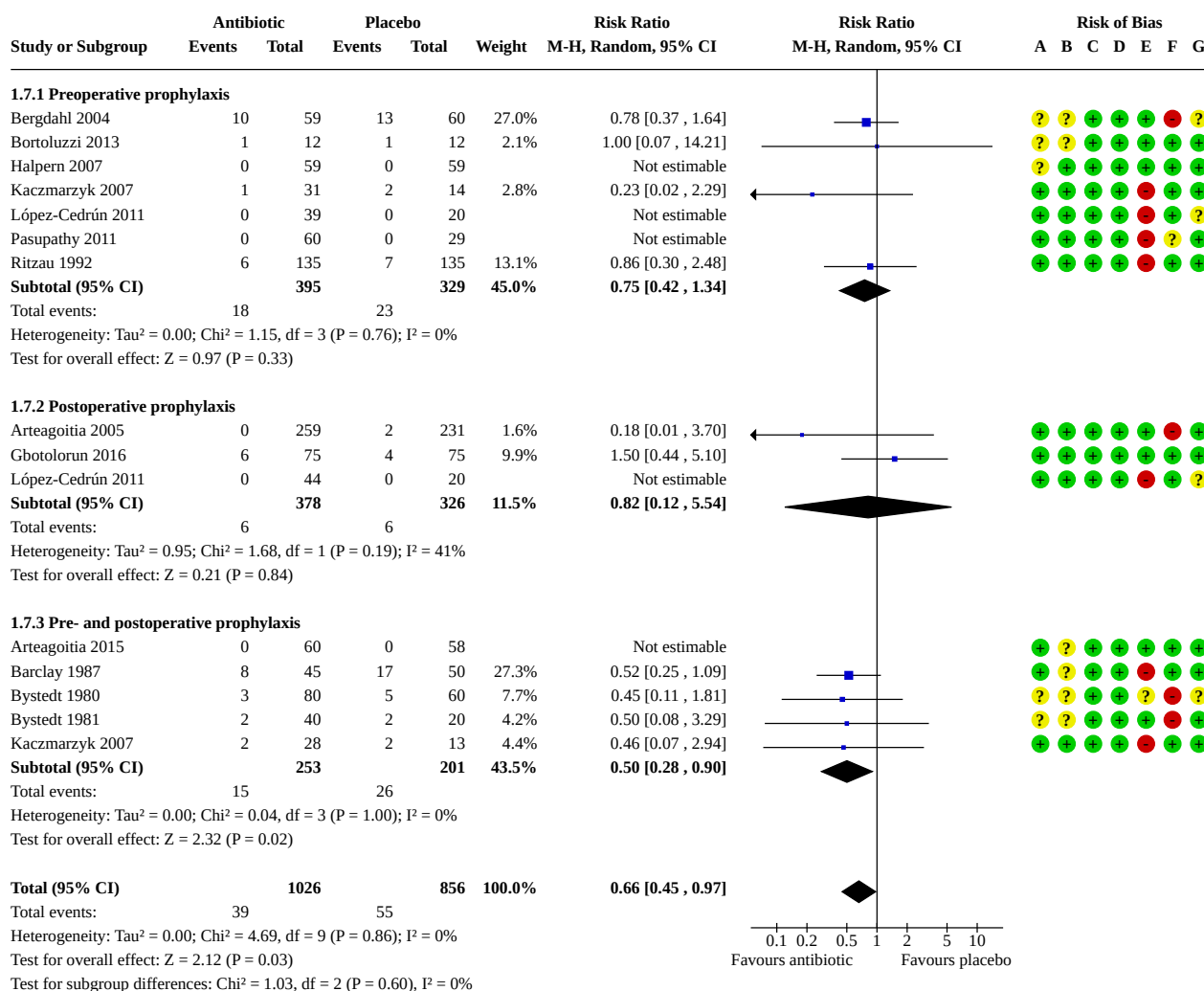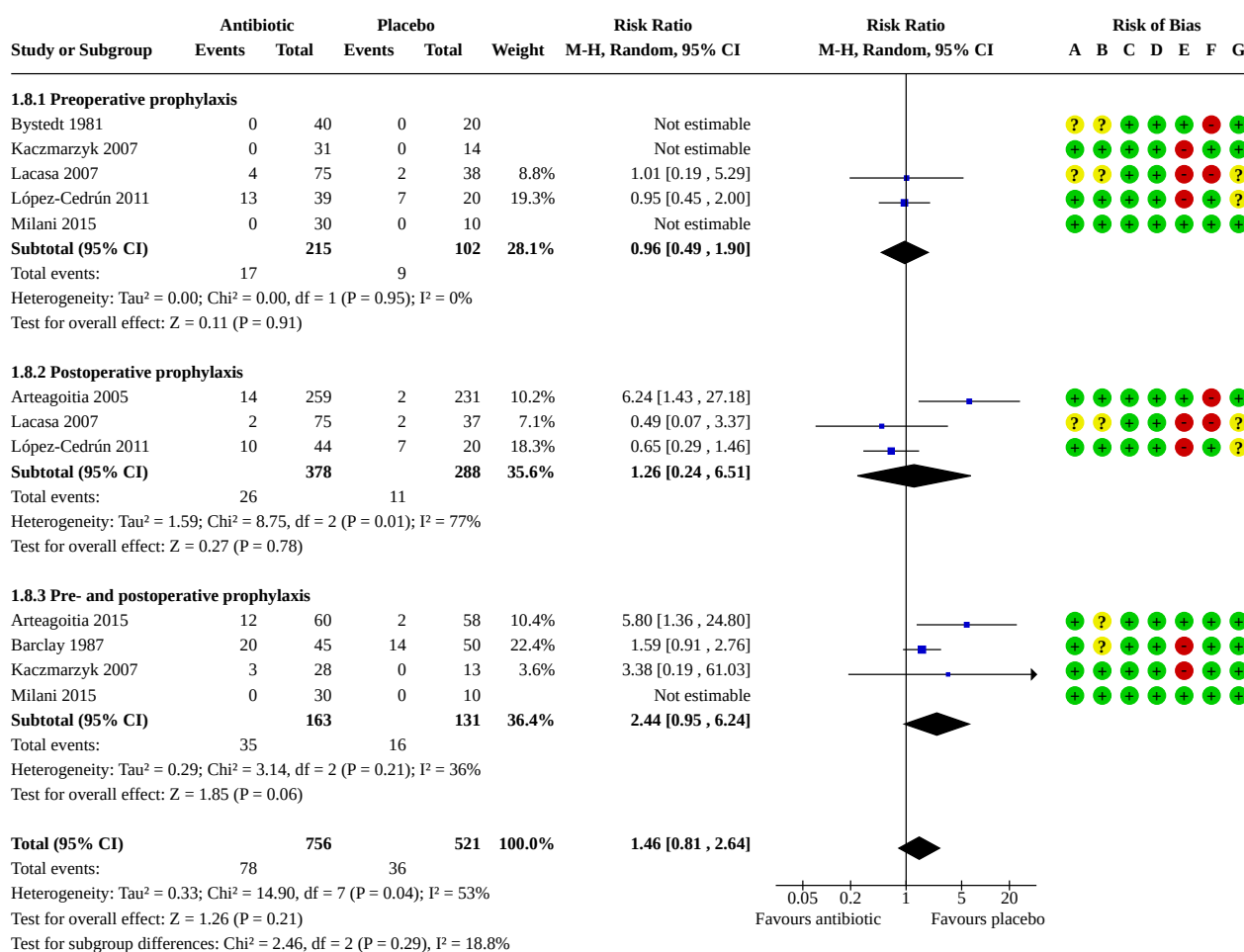### Analysis 1.8.   Comparison 1: Antibiotic versus placebo, Outcome 8: Adverse events (6th to 7th day)

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Preoperative prophylaxis						
Bystedt 1981	0	40	0	20		Not estimable
Kaczmarzyk 2007	0	31	0	14		Not estimable
Lacasa 2007	4	75	2	38	8.8%	1.01 [0.19 , 5.29]
López-Cedrún 2011	13	39	7	20	19.3%	0.95 [0.45 , 2.00]
Milani 2015	0	30	0	10		Not estimable
Subtotal (95% CI)		**215**		**102**	**28.1%**	**0.96 [0.49 , 1.90]**
Total events:	17		9			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)

1.8.2 Postoperative prophylaxis						
Arteagoitia 2005	14	259	2	231	10.2%	6.24 [1.43 , 27.18]
Lacasa 2007	2	75	2	37	7.1%	0.49 [0.07 , 3.37]
López-Cedrún 2011	10	44	7	20	18.3%	0.65 [0.29 , 1.46]
Subtotal (95% CI)		**378**		**288**	**35.6%**	**1.26 [0.24 , 6.51]**
Total events:	26		11			

Heterogeneity: Tau² = 1.59; Chi² = 8.75, df = 2 (P = 0.01); I² = 77%
Test for overall effect: Z = 0.27 (P = 0.78)

1.8.3 Pre- and postoperative prophylaxis						
Arteagoitia 2015	12	60	2	58	10.4%	5.80 [1.36 , 24.80]
Barclay 1987	20	45	14	50	22.4%	1.59 [0.91 , 2.76]
Kaczmarzyk 2007	3	28	0	13	3.6%	3.38 [0.19 , 61.03]
Milani 2015	0	30	0	10		Not estimable
Subtotal (95% CI)		**163**		**131**	**36.4%**	**2.44 [0.95 , 6.24]**
Total events:	35		16			

Heterogeneity: Tau² = 0.29; Chi² = 3.14, df = 2 (P = 0.21); I² = 36%
Test for overall effect: Z = 1.85 (P = 0.06)

Total (95% CI)		**756**		**521**	**100.0%**	**1.46 [0.81 , 2.64]**
Total events:	78		36			

Heterogeneity: Tau² = 0.33; Chi² = 14.90, df = 7 (P = 0.04); I² = 53%
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Chi² = 2.46, df = 2 (P = 0.29), I² = 18.8%

0.05   0.2   1   5   20
Favours antibiotic   Favours placebo

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

ADDITIONAL TABLES

Table 1.   Studies of reasons for tooth extraction

Author	Country	% for caries	% for periodontitis
Da'ameh 2006	Afghanistan	59.2	35.3
Akhter 2008	Bangladesh	67.5	18.5
Jovino-Silveira 2005	Brazil	63.3	13.1
Chrysanthakopoulos 2011	Greece	45.6	32.1

Table 1. Studies of reasons for tooth extraction *(Continued)*

Anand 2010	India	44.6	33.2
Jafarian 2013	Iran	51	14.4
Passarelli 2020	Italy	52.2	35.7
Aida 2009	Japan	43.6	37.1
Baqain 2007	Jordan	63.8	22.9
Al-Shammari 2006	Kuwait	43.7	37.4
Byahatti 2011	Libya	55.9	34.4
Danielson 2011	Nigeria	32.6	45
Trovik 2000	Norway	40	24
Chestnutt 2000	Scotland	51	21
McCaul 2001	Scotland	54.7	16.7
Lesolang 2009	South Africa	47.9	22.6
Lee 2015	Taiwan	55.3	22.1
Jamghili 2016	USA	73	10
Richards 2005	Wales	59	29.1

Table 2. Raw outcome data - postsurgical infectious complications

Infection (%)

	Antibiotic	Placebo
Preoperative prophylaxis		
Mitchell 1986	4/25 (16%)	14/25 (56%)
Sekhar 2001	1/44 (2%)	0/17
Lacasa 2007*	4/68 (5.9%)	3/31 (9.7%)
Halpern 2007	0/59	5/59 (8%)
López-Cedrún 2011	0/39	3/20 (15%)
Pasupathy 2011	2/60 (3%)	3/29 (10%)
Bortoluzzi 2013	0/12	0/12
Bezerra 2011 (split-mouth cross-over)	0/34	3/34

Table 2.   Raw outcome data - postsurgical infectious complications *(Continued)*

Postoperative prophylaxis

Sekhar 2001	0/47	0/17
Arteagoitia 2005	2/259 (0.8%)	22/231 (9.6%)
Lacasa 2007*	2/69 (2.9%)	3/31 (9.7%)
López-Cedrún 2011	0/44	2/20 (10%)
Gbotolorun 2016	1/75 (1.3%)	0/75
Pre- and postoperative prophylaxis		
Happonen 1990	11/91 (12%)	5/45 (11%)
Leon Arcila 2001	0/49	0/53
Arteagoitia 2015	0/60	1/58 (1.7%)
Frequency of infection per group	27/1035 (2.6%)	64/757 (8.5%)

*In this study dry socket was reported amongst postsurgical infectious complications.

Table 3.   Raw outcome data - pain (dichotomous) day 6 to 7

Pain (dichotomous) day 6 to 7

	Antibiotic	Placebo
Preoperative prophylaxis		
Sekhar 2001	20/44 (45.5%)	7/17 (41.2%)
Postoperative prophylaxis		
Sekhar 2001	17/47 (36.2%)	8/17 (47.1%)
Arteagoitia 2005	4/259 (1.5%)	14/231 (6%)
Pre- and postoperative prophylaxis		
Bystedt 1981	5/40 (12.5%)	7/20 (35%)
Frequency of pain per group	46/390 (11.8%)	36/285 (12.6%)

Table 4.   Raw outcome data - pain (continuous, measured by VAS) at day 6 to 7

Mean (SD) VAS pain scores

	Antibiotic	Placebo
Preoperative prophylaxis		

Table 4. Raw outcome data - pain (continuous, measured by VAS) at day 6 to 7 *(Continued)*

Kaczmarzyk 2007	0.95 (2.4)	1.01 (1.9)
	n = 31	n = 27
Sekhar 2001	2.4 (0.7)	2.5 (0.6)
	n = 44	n = 34
Bezerra 2011 (split-mouth cross-over study)	1.59 (2.36)	3.12 (2.95)
	n = 34	n = 34
Postoperative prophylaxis		
Sekhar 2001	2.6 (0.5)	2.5 (0.6)
	n = 47	n = 34
Pre- and postoperative prophylaxis		
Arteagoitia 2015	1.1 (2.0)	1.8 (2.1)
	n = 59	n = 57
Barclay 1987*	0.63 (1.25)	1.48 (2.2)
	n = 45	n = 50
Kaczmarzyk 2007	0.39 (0.98)	1.01 (1.9)
	n = 28	n = 27

*Participants in this study had some pericoronitis in the recent past and were therefore at higher risk of infection.
SD = standard deviation; VAS = visual analogue scale.

Table 5. Raw outcome data - fever at day 6 to 7

Fever at day 6 to 7		
	Antibiotic	Placebo
Preoperative prophylaxis		
Lacasa 2007	0/68	0/31
Milani 2015	0/30	0/10
Postoperative prophylaxis		
Bystedt 1981	0/40	0/20
Happonen 1990	8/91 (8.8%)	6/45 (13.3%)
Lacasa 2007	0/69	0/31
Pre- and postoperative prophylaxis		

Table 5. Raw outcome data - fever at day 6 to 7 *(Continued)*

Milani 2015	0/30	0/10
Frequency of fever per group	8/328 (2.4%)	6/147 (4.1%)

Table 6. Raw data - swelling at day 6 to 7

Swelling at day 6 to 7

	Antibiotic	Placebo
Preoperative prophylaxis		
Sekhar 2001	21/44 (47.7%)	7/17 (41.2%)
Kaczmarzyk 2007	9/31 (29.0%)	2/14 (14.3%)
López-Cedrún 2011	10/39 (25.6%)	6/20 (30.0%)
Postoperative prophylaxis		
Sekhar 2001	11/47 (23.4%)	8/17 (47.1%)
López-Cedrún 2011	13/44 (29.5%)	6/20 (30.0%)
Pre- and postoperative prophylaxis		
Kaczmarzyk 2007	6/28 (21.4%)	2/13 (15.4%)
Arteagoitia 2015	4/60 (6.7%)	16/58 (27.6%)
Frequency of swelling per group	74/293 (25.3%)	47/159 (29.6%)

Table 7. Raw data - trismus at day 6 to 7

Trismus at day 6 to 7

	Antibiotic	Placebo
Preoperative prophylaxis		
Kaczmarzyk 2007	7/31 (22.6%)	3/14 (21.4%)
Pasupathy 2011	5/60 (8.3%)	4/29 (13.8%)
Bortoluzzi 2013	3/12 (25%)	5/12 (41.7%)
Pre- and postoperative prophylaxis		
Kaczmarzyk 2007	6/28 (21.4%)	3/13 (23.1%)
Frequency of trismus per group	21/131 (16.0%)	15/68 (22.1%)

Table 8.   Raw data - dry socket

Dry socket		
	Antibiotic	Placebo
Preoperative prophylaxis		
Ritzau 1992	6/135 (4.4%)	7/135 (5.2%)
Bergdahl 2004	10/59 (16.9%)	13/60 (21.7%)
Kaczmarzyk 2007	1/31 (3.2%)	2/14 (14.3%)
Halpern 2007	0/59	0/59
López-Cedrún 2011	0/39	0/20
Pasupathy 2011	0/60	0/29
Bortoluzzi 2013	1/12 (8.3%)	1/12 (8.3%)
Bezerra 2011 (split-mouth cross-over)	1/34 (2.9%)	1/34 (2.9%)
Postoperative prophylaxis		
Arteagoitia 2005	0/259	2/231 (0.9%)
López-Cedrún 2011	0/44	0/20
Gbotolorun 2016	6/75 (8.0%)	4/75 (5.3%)
Pre- and postoperative prophylaxis		
Bystedt 1980	3/80 (3.8%)	5/60 (8.3%)
Bystedt 1981	2/40 (5.0%)	2/20 (10.0%)
Barclay 1987	8/45 (17.8%)	17/50 (34.0%)
Kaczmarzyk 2007	2/28 (7.1%)	2/13 (15.4%)
Arteagoitia 2015	0/60	0/58
Frequency of dry socket per group	40/1060 (3.8%)	56/890 (6.3%)

Table 9.   Raw data - adverse effects

Adverse effects		
	Antibiotic	Placebo
Preoperative prophylaxis		

Table 9. Raw data - adverse effects *(Continued)*

Bystedt 1981	0/40	0/20
Kaczmarzyk 2007	0/31	0/14
Lacasa 2007	4/75 (5.3%)	2/38 (5.3%)
López-Cedrún 2011	13/39 (33.3%)	7/20 (35.0%)
Milani 2015	0/30	0/10
Postoperative prophylaxis		
Arteagoitia 2005	14/259 (5.4%)	2/231 (0.9%)
Lacasa 2007	2/75 (2.7%)	2/37 (5.4%)
López-Cedrún 2011	10/44 (22.7%)	7/20 (35.0%)
Pre- and postoperative prophylaxis		
Barclay 1987	20/45 (44.4%)	14/50 (28.0%)
Kaczmarzyk 2007	3/28 (10.7%)	0/13
Arteagoitia 2015	12/60 (20.0%)	2/58 (3.4%)
Milani 2015	0/30	0/10
Frequency of adverse effects per group	78/756 (10.3%)	36/521 (6.9%)

Table 10. Nature of adverse effects when in studies as an outcome

Study	Adverse effects
Arteagoitia 2005	Nausea/vomiting, diarrhoea, abdominal pain, candidiasis
Arteagoitia 2015	Nausea/vomiting, diarrhoea, abdominal pain, candidiasis, others
Barclay 1987	Nausea/vomiting, headache, altered taste, drowsiness, dizziness
Bystedt 1981	None recorded.
Kaczmarzyk 2007	Abdominal pain
Lacasa 2007	Diarrhoea, headache
López-Cedrún 2011	Nausea/vomiting, diarrhoea, abdominal pain, headache, rash, others
Milani 2015	None recorded.

A P P E N D I C E S

Appendix 1. Cochrane Oral Health Trials Register search strategy

Cochrane Oral Health's Trials Register is available via the Cochrane Register of Studies. For information on how the register is compiled, see oralhealth.cochrane.org/trials

From February 2019, searches of the Cochrane Oral Health Trials Register were undertaken via the Cochrane Register of Studies, using the search strategy below:

1 MESH DESCRIPTOR Tooth Extraction EXPLODE ALL AND INREGISTER
2 exodontia AND INREGISTER
3 ((tooth near/4 extract*) or (teeth near/4 extract*) or ("third molar*" near/4 extract*) or (3rd and (molar* near/4 extract*)) or "dental extract*" or (tooth near/4 remov*) or (teeth near/4 remov*) or ("third molar*" near/4 remov*) or ("3rd molar*" near/4 remov*) or (tooth near/4 surg*) or (teeth near/4 surg*) or ("third molar*" near/4 surg*) or ("3rd molar*" near/4 surg*)) AND INREGISTER
4 #1 or #2 or #3
5 MESH DESCRIPTOR Molar EXPLODE ALL AND INREGISTER
6 MESH DESCRIPTOR Tooth, Impacted AND INREGISTER
7 ("wisdom tooth" or "wisdom teeth" or (third near/3 molar)) AND INREGISTER
8 "impacted tooth" AND INREGISTER
9 "impacted teeth" AND INREGISTER
10 (#5 or #6 or #7 or #8 or #9)
11 (extract* or remov* or surg*) AND INREGISTER
12 (#10 and #11)
13 (#4 or #12)
14 MESH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL AND INREGISTER
15 MESH DESCRIPTOR Antibiotic prophylaxis AND INREGISTER
16 MESH DESCRIPTOR Erythromycin EXPLODE ALL AND INREGISTER
17 MESH DESCRIPTOR Metronidazole AND INREGISTER
18 MESH DESCRIPTOR Tetracyclines AND INREGISTER
19 MESH DESCRIPTOR Clindamycin AND INREGISTER
20 MESH DESCRIPTOR Teicoplanin AND INREGISTER
21 MESH DESCRIPTOR Vancomycin AND INREGISTER
22 MESH DESCRIPTOR Floxacillin AND INREGISTER
23 MESH DESCRIPTOR Gentamicins AND INREGISTER
24 MESH DESCRIPTOR Cephalexin AND INREGISTER
25 (antibiot* or "anti biot*" or anti-biot*) AND INREGISTER
26 (penicillin* or erythromycin* or metronidazol* or cephalosporin*) AND INREGISTER
27 (sulphonamide* or tetracycline* or clindamycin* or clindamicin* or augmentin* or flagyl* or amoxyl* or amoxil* or co-amox* or antifungal* or anti-fungal* or "anti fungal*" or teicoplanin* or vancomycin* or vancomicin* or flucloxacillin* or floxacillin* or gentamicin* or gentamycin* or cephalexin*) AND INREGISTER
28 (antibacterial or anti-bacterial or "anti bacterial") AND INREGISTER
29 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
30 (#13 and #29)

Previous searches of the register were undertaken via the Procite software, using the search strategy below:

((extract* or remov* or exodontia or "impacted teeth" or "impacted tooth" or "oral surg*" or (tooth and surg*) or (teeth and surg*) or ("third molar*" and surg*)) AND (antibiotic* or erthromycin* or metronidaz* or tetracycline* or clindamycin* or teicoplanin* or vancomycin* or floxacillin* or gentamicin* or cephalexin* or "anti biotic*" or anti-biotic* or penicillin* or antibacterial* or anti-bacterial* or "anti bacterial*" or erthromycin* or cephalsporin* or suphonamide* or clindamicin* or augmentin* or flagyl* or amoxyl* or amoxil* co-amox* or antifungal* or anti-fungal* or "anti fungal*" or vancomicin* or flucloxacillin* or floxacillin* or gentamycin* or cephalexin*))

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1   MeSH descriptor Tooth extraction explode all trees
#2   exodontia in All Text
#3   ((tooth in All Text near/4 extract* in All Text) or (teeth in All Text near/4 extract* in All Text) or ("third molar*" in All Text near/4 extract* in All Text) or (3rd in All Text and (molar* in All Text near/4 extract* in All Text)) or "dental extract*" in All Text or (tooth in All Text near/4 remov* in All Text) or (teeth in All Text near/4 remov* in All Text) or ("third molar*" in All Text near/4 remov* in All Text) or ("3rd molar*" in All Text near/4 remov* in All Text) or (tooth in All Text near/4 surg* in All Text) or (teeth in All Text near/4 surg* in All Text) or ("third molar*" in All Text near/4 surg* in All Text) or ("3rd molar*" in All Text near/4 surg* in All Text))
#4   (#1 or #2 or #3)
#5   MeSH descriptor Molar explode all trees

#6   MeSH descriptor Tooth, impacted this term only
#7   ("wisdom tooth" in All Text or "wisdom teeth" in All Text or (third in All Text near/3 molar in All Text))
#8   "impacted tooth" in All Text
#9   "impacted teeth" in All Text
#10   (#5 or #6 or #7 or #8 or #9)
#11   (extract* in All Text or remov* in All Text or surg* in All Text)
#12   (#10 and #11)
#13   (#4 or #12)
#14   MeSH descriptor Anti-Bacterial Agents explode all trees
#15   MeSH descriptor Antibiotic prophylaxis this term only
#16   MeSH descriptor Erythromycin explode all trees
#17   MeSH descriptor Metronidazole this term only
#18   MeSH descriptor Tetracyclines this term only
#19   MeSH descriptor Clindamycin this term only
#20   MeSH descriptor Teicoplanin this term only
#21   MeSH descriptor Vancomycin this term only
#22   MeSH descriptor Floxacillin this term only
#23   MeSH descriptor Gentamicins this term only
#24   MeSH descriptor Cephalexin this term only
#25   (antibiot* in All Text or "anti biot*" in All Text or anti-biot* in All Text)
#26   (penicillin* in All Text or erythromycin* in All Text or metronidazol* in All Text or cephalosporin* in All Text)
#27   (sulphonamide* in All Text or tetracycline* in All Text or clindamycin* in All Text or clindamicin* in All Text or augmentin* in All Text or flagyl* in All Text or amoxyl* in All Text or amoxil* in All Text or co-amox* in All Text or antifungal* in All Text or anti-fungal* in All Text or "anti fungal*" in All Text or teicoplanin* in All Text or vancomycin* in All Text or vancomicin* in All Text or flucloxacillin* in All Text or floxacillin* in All Text or gentamicin* in All Text or gentamycin* in All Text or cephalexin* in All Text)
#28   (antibacterial in All Text or anti-bacterial in All Text or "anti bacterial" in All Text)
#29   (#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28)
#30   (#13 and #29)

Appendix 3. MEDLINE Ovid search strategy

1.   exp TOOTH EXTRACTION/
2.   exodontia.mp.
3.   ((tooth adj4 extract$) or (teeth adj4 extract$) or ("third molar$" adj4 extract$) or ("3rd molar$" adj4 extract$) or "dental extract$" or (tooth adj4 remov$) or (teeth adj4 remov$) or ("third molar$" adj4 remov$) or ("third molar$" adj4 remov$) or (tooth adj4 surg$) or (teeth adj4 surg$) or ("third molar$" adj4 surg$) or ("3rd molar$" adj4 surg$)).mp.
4.   1 or 2 or 3
5.   MOLAR/
6.   TOOTH IMPACTED/
7.   ("wisdom tooth" or "wisdom teeth" or (third adj3 molar$) or (3rd adj3 molar$)).mp.
8.   "impacted tooth".mp.
9.   "impacted teeth".mp.
10.   (5 or 6 or 7 or 8 or 9) and (extract$ or remov$ or surg$).mp.
11.   10 or 4
12.   exp ANTIBIOTICS/
13.   ANTIBIOTIC PROPHYLAXIS/
14.   ERYTHROMYCIN/
15.   METRONIDAZOLE/
16.   TETRACYCLINES/
17.   CLINDAMYCIN/
18.   TEICOPLANIN/
19.   VANCOMYCIN/
20.   FLOXACILLIN/
21.   GENTAMICINS/
22.   CEPHALEXIN/
23.   (Antibiot$ or "anti biot$" or anti-biot$).mp.
24.   (penicillin$ or erythromycin$ or Metronidazol$ or Cephalosporin$).mp.
25.   (antibacterial or anti-bacterial or "anti bacterial").mp.
26.   (sulphonamide$ or tetracycline$ or clindamycin$ or clindamicin$ or augmentin$ or flagyl$ or amoxyl$ or amoxil$ or co-amox$ or antifungal$ or anti-fungal$ or "anti fungal$" or teicoplanin$ or vancomycin$ or vancomicin$ or flucloxacillin or floxacillin or gentamicin$ or gentamycin$ or cephalexin$).mp.
27.   or/12-26

28.   27 and 11

This subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision) as referenced in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of InterventionsVersion 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook (Lefebvre 2019).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 4. Embase Ovid search strategy

1.   exp TOOTH EXTRACTION/
2.   exodontia.ti,ab.
3.   ((tooth adj4 extract$) or (teeth adj4 extract$) or ("third molar$" adj4 extract$) or ("3rd molar$" adj4 extract$) or "dental extract$" or (tooth adj4 remov$) or (teeth adj4 remov$) or ("third molar$" adj4 remov$) or ("third molar$" adj4 remov$) or (tooth adj4 surg$) or (teeth adj4 surg$) or ("third molar$" adj4 surg$) or ("3rd molar$" adj4 surg$)).ti,ab.
4.   1 or 2 or 3
5.   exp TOOTH/
6.   ("wisdom tooth" or "wisdom teeth" or (third adj3 molar$) or (3rd adj3 molar$)).ti,ab.
7.   "impacted tooth".ti,ab.
8.   "impacted teeth".ti,ab.
9.   or/5-8
10.   (extract$ or remov$ or surg$).ti,ab.
11.   9 and 10
12.   4 or 11
13.   exp ANTIBIOTIC AGENT/
14.   ANTIBIOTIC PROPHYLAXIS/
15.   METRONIDAZOLE/
16.   (Antibiot$ or "anti biot$" or anti-biot$).ti,ab.
17.   (penicillin$ or erythromycin$ or Metronidazol$ or Cephalosporin$).ti,ab.
18.   (antibacterial or anti-bacterial or "anti bacterial").ti,ab.
19.   (sulphonamide$ or tetracycline$ or clindamycin$ or clindamicin$ or anti-fungal$ or "anti fungal$" or teicoplanin$ or vancomycin$ or vancomicin$ or flucloxacillin or floxacillin or gentamicin$ or gentamycin$ or cephalexin$).ti,ab.
20.   or/13-19
21.   12 and 20

This subject search was linked to the Cochrane search filter for identifying randomised trials in Embase (2016 version) as referenced in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of InterventionsVersion 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook (Lefebvre 2019)

1. Randomized controlled trial/
2. Controlled clinical study/
3. random$.ti,ab.
4. randomization/
5. intermethod comparison/
6. placebo.ti,ab.
7. (compare or compared or comparison).ti.
8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
9. (open adj label).ti,ab.
10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

11. double blind procedure/

12. parallel group$1.ti,ab.

13. (crossover or cross over).ti,ab.

14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.

15. (assigned or allocated).ti,ab.

16. (controlled adj7 (study or design or trial)).ti,ab.

17. (volunteer or volunteers).ti,ab.

18. human experiment/

19. trial.ti.

20. or/1-19

21. random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)

22. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

23. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

24. (Systematic review not (trial or study)).ti.

25. (nonrandom$ not random$).ti,ab.

26. "Random field$".ti,ab.

27. (random cluster adj3 sampl$).ti,ab.

28. (review.ab. and review.pt.) not trial.ti.

29. "we searched".ab. and (review.ti. or review.pt.)

30. "update review".ab.

31. (databases adj4 searched).ab.

32. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

33. Animal experiment/ not (human experiment/ or human/)

34. or/21-33

35. 20 not 34

Appendix 5. LILACS BIREME Virtual Health Library search strategy

(Mh Tooth extraction or Mh Extracción Dental or Mh Extração Dentária or ((Tw tooth or Tw teeth or Tw molar$ or Tw dental) and (Tw extrac$ or Tw remov$ or Tw surg$))) [Words] and (Mh Anti-Bacterial Agents or Mh Agentes Antibacterianos or Mh Antibiotic Prophylaxis or Profilaxis Antibiótica or Mh Antibioticoprofilaxia or antibiot$ or "anti biot$" or anti-biot$ or antibacte$ or anti-bacte$ or "anti bacte$" or penicillin$ or erythromycin$ or metronidazol$ or cephalosporin$ or sulphonamide$ or tetracycline$ or clindamycin$ or clindamicin$ or augmentin$ or flagyl$ or amoxyl$ or amoxil$ or co-amox$ or teicoplanin$ or vancomycin$ or vancomicin$ or flucloxacillin$ or floxacillin$ or gentamicin$ or gentamycin$ or cephalexin$) [Words]

The above subject search was linked to the Brazilian Cochrane Center filter for LILACs via BIREME:

Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple $ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) and not (Ct ANIMAL AND NOT (Ct HUMAN and Ct ANIMAL)))

Appendix 6. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov search strategy

Expert search (filter: Interventional studies)

(tooth extraction OR tooth removal OR exodontia OR "impacted teeth" OR "impacted tooth") AND (antibiotic OR erthromycin OR metronidaz OR tetracycline OR clindamycin OR teicoplanin OR vancomycin OR floxacillin OR gentamicin OR cephalexin OR "anti biotic" OR anti-biotic OR penicillin OR antibacterial OR anti-bacterial OR "anti bacterial" OR erthromycin OR cephalsporin OR suphonamide OR clindamicin OR augmentin OR flagyl OR antifungal OR anti-fungal OR "anti fungal" OR vancomicin OR flucloxacillin OR floxacillin OR gentamycin OR cephalexin)

Appendix 7. World Health Organization International Clinical Trials Registry Platform search strategy

tooth AND removal AND antibiotic OR tooth AND extraction AND antibiotic OR tooth AND remove AND antibiotic OR tooth AND extract AND antibiotic

tooth AND removal AND antibacterial OR tooth AND extraction AND antibacterial OR tooth AND remove AND antibacterial OR tooth AND extract AND antibacterial

tooth AND removal AND metronidazole OR tooth AND extraction AND metronidazole OR tooth AND remove AND metronidazole OR tooth AND extract AND metronidazole

tooth AND removal AND penicillin OR tooth AND extraction AND penicillin OR tooth AND remove AND penicillin OR tooth AND extract AND penicillin

FEEDBACK

Comment from Dr John Curran, 11 February 2013

Summary

Very good review. Unfortunately the difficulty of designing a randomised trial still exists partly due to ethical requirements and logistics - e.g. with third molar surgery assessment of difficulty and surgical ability are hard to measure. Post-operative assessment also needs to be done sooner than the 7 days used in the review. Little has changed in but I believe that in patient age groups most prevalent in the North America context the incidence of infection is even lower than reported -i.e. antibiotic usage should be highly selective.

Reply

Thank you for your interest in our work and for your comment.
I absolutely agree that real incidence of infectious complications in a population similar to study groups is likely to be lower, and for that reason we did not really recommend for regular antibiotic prophylaxis. Unfortunately because of the lack of studies on patients at higher risk, no evidence is available on cases for which antibiotic prophylaxis is (anecdotally) recommended.

Contributors

Summary: John Curran.
Reply: Giovanni Lodi.

WHAT'S NEW

Date	Event	Description
31 October 2020	New citation required but conclusions have not changed	Each section of the review was updated, with particular attention paid to the Background, Secondary outcomes, Results, and Discussion. Five new randomised controlled trials were identified and added, with new results. However, the conclusions of the review were not changed from the first version.
16 April 2020	New search has been performed	New search run and five new studies identified.

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 11, 2012

Date	Event	Description
24 April 2013	Feedback has been incorporated	Comment from Dr John Curran

CONTRIBUTIONS OF AUTHORS

- Conceiving, designing, and co-ordinating the review: Giovanni Lodi (GL), Elena Varoni (EV), Lorenzo Azzi (LA), Monica Pentenero (MP), Maddalena Manfredi (MM).
- Screening search results and retrieved papers against the inclusion criteria: GL, EV, LA, MP, MM.
- Appraising the quality of papers: GL, MM, EV, LA, MP.
- Extracting data from papers: GL, LA, EV, MP, MM, Andrea Sardella (AS).
- Writing to authors of papers for additional information: GL, LA; AS, Antonio Carrassi (AC).
- Data management for the review and entering data into Review Manager 5: GL, LA, EV, MP, MM.
- Analysis and interpretation of data: GL, EV, LA, MP, MM.
- Preparing the 'Summary of findings' table: GL, LA, EV, MP, MM.
- Providing a clinical perspective: GL, LA, EV, MP, MM, Massimo Del Fabbro (MDF).
- Writing the text of the review: GL, EV, LA, MP, MM.
- Preparing the Plain language summary: GL, AS, AC, MDF.
- Providing comments on a draft of the review: GL, EV, LA, MP, MM, AC, MDF, AS.

DECLARATIONS OF INTEREST

GL: none
LA: none
EV: none
MP: none
MDF: none
AC: none
AS: none
MM: none

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Quasi-randomised studies are no longer eligible for inclusion in the review because less biased evidence is available from randomised controlled trials.

We decided to include only double-blind, placebo-controlled studies because we believe that these studies are likely to provide the best evidence to inform practice.

We clarified that we were excluding trials where the only outcomes were endocarditis incidence, bacteraemia, or serum marker of infection.

Some of the secondary outcomes (persistence of pain, presence of swelling, trismus, fever) were considered at six to seven days after dental surgery as possible symptoms or signs of infection. Their presence before this timing could not be considered as a real complication of the intervention but possibly due to the surgical trauma.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [adverse effects] [*therapeutic use]; *Antibiotic Prophylaxis [adverse effects]; Bacterial Infections [prevention & control]; Bias; Controlled Clinical Trials as Topic; Dry Socket [prevention & control]; Molar, Third [*surgery]; Pain, Postoperative [prevention & control]; Postoperative Complications [*prevention & control]; Tooth Extraction [*adverse effects]; Tooth, Impacted [*surgery]

MeSH check words

Humans